June 1994
Volume 39, Number 6
ISSN 00989142-RECACP

RESPIRATORY CARE

A MONTHLY SCIENCE JOURNAL
39TH YEAR—ESTABLISHED 1956

- Imposed Work of Breathing with Endotracheal vs Tracheostomy Tubes
- Evaluation of Aerosol Controller during Simulated Volume-Controlled Ventilation
- Determining Intrinsic PEEP with the Siemens 900C
- Bezold-Jarisch Reflex: A Case Report
- Vocal Cord Paralysis in a Newborn Infant: A Case Report
- Cerebral Gas Embolism: A Review and Update

AARC
40th Annual Convention and Exhibition
December 10-13, 1994 • Las Vegas, Nevada

SIEMENS

Now even the tiniest engine can generate airspeed.

MED-1004248 3691 ©Siemens Medical Systems, Inc. 1994

When your little patient makes even the slightest inspiratory effort, the flow triggering function of the Servo Ventilator 300® will respond. And in record time!

One of the fastest, most sensitive gas delivery methods available in patient care today, flow triggering works in all modes for all patients. An advantage that few others can offer.

In addition to flow triggering, all exclusive features available with the Servo Ventilator 300 are applicable to neonatal, pediatric, and adult patients alike.

We live and breathe patient care.

Siemens brings you the very best in ventilator care. For more information on the Servo Ventilator 300, or to arrange a personal demonstration, contact your local Siemens representative.

Siemens Medical Systems, Inc.
Electromedical Group
16 Electronics Avenue
Danvers, MA 01923
Toll-Free 1-800-333-8646

Siemens...
technology in caring hands.

Circle 103 on reader service card

Promoting Respiratory Care

Decisions

This dynamic eight-page booklet is designed especially to help young adults make respiratory care their career decision. Each page presents information on the practice of respiratory care, the skills used, patients, working conditions, job prospects, qualifications, and training. This exciting color booklet will fill classrooms with eager young adults on their way to a challenging career. **Item PR12. $20, Pkg 50** (Member $10)

"Hello, I'm Your Respiratory Care Practitioner"

It's a greeting that says what this brochure does best: introduces you and respiratory care. This six-page brochure not only introduces you, but describes what you do — from diagnosis, to treatment, to education, and to training. Packed with information to provide to your potients or other hospital staff. **Item PR11. $20, Pkg 50** (Member $10)

Transitions

Fill your respiratory care program with those wanting a change to a more rewarding job with this eight-page booklet. Its full-color pictures illustrate the compassion, challenge, and rewards of a career in respiratory care. Focuses on the practice of respiratory care, the practitioner's many skills, patients, working conditions, job prospects, qualifications, and training. **Item PR13. $20, Pkg 50** (Member $10)

Orders with credit cards or P.O. numbers may call (214) 243-2272, or Fax to (214) 484-2720. If ordering by mail, send coupon to.
AARC Order Department, 11030 Ables Lane, Dallas, Texas 75229-4593.

Allow One Day for Order Processing for Regular and Express Shipping Addresses outside the continental U.S. — Provide telephone number and contact for shipping quote.

Order Total	UPS Reg.	UPS 2nd Day	UPS Next Day
$15 or less	3.25	6.00	14.00
$16 to $30	3.75	8.00	18.00
$31 to $50	4.50	11.00	24.00
$51 to $75	5.50	13.00	31.00
$76 to $100	7.00	16.00	38.00
$101 to $125	8.00	19.00	50.00
$126 to $150	10.00	22.00	60.00
$151 or more	12.00	27.00	75.00

Please send me the items I have indicated below.

Item	Description	Quantity	Price Each	Total Price

Ship via UPS ☐ Ground ☐ 2nd Day Air ☐ Next Day Air
Please use the chart at left to calculate shipping.

Shipping _____
Merchandise _____
TOTAL _____

☐ Check or Money Order enclosed payable to the AARC
☐ Bill me, my P.O. # is _____
☐ Charge to my ☐ Visa ☐ MasterCard
Card # _____ Exp. Date _____ Signature _____
AARC Member # _____ Name _____
Institution _____
Address _____ City/State/Zip _____

"Our patients are mastering SMI therapy in almost no time. That's why I'll choose Coach® every time. Thanks, DHD."

Brenda Kalette, RRT

With the DHD Coach incentive spirometer, accurate SMI therapy is simplified for respiratory patients and clinicians alike. An exclusive combination of features helps "coach" patients to inhale properly, maintain correct inspiratory flowrate, and easily monitor their own progress. For more information on Coach, a free patient training video, or the entire line of DHD quality respiratory care products, please call DHD toll-free at

1•800•847•8000

DHD
DIEMOLDING HEALTHCARE DIVISION

Canastota, NY 13032 USA
(800) 847-8000 FAX (315) 697-8083
(315) 697-2221

Circle 94 on reader service card

RESPIRATORY CARE

A Monthly Science Journal. Established 1956. Official Journal of the American Association for Respiratory Care.

EDITORIAL OFFICE
11030 Ables Lane
Dallas TX 75229
(214) 243-2272

EDITOR
Pat Brougher BA RRT

ASSOCIATE EDITOR
Kaye Weber MS RRT

ASSISTANT EDITOR
Donna Stephens BBA

MANAGING EDITOR
Ray Masferrer BA RRT

EDITORIAL BOARD
Dean Hess MEd RRT, Chairman
Thomas A Barnes EdD RRT
Richard D Branson RRT
Crystal L Dunlevy EdD RRT
Charles G Durbin Jr MD
Thomas D East PhD
Neil R MacIntyre MD
Shelley C Mishoe MEd RRT
Joseph L Rau PhD RRT
James K Stoller MD

CONSULTING EDITORS
Frank E Biondo BS RRT
Howard J Birenbaum MD
Robert L Chatburn RRT
Patricia Ann Doorley MS RRT
Donald R Elton MD
Robert R Fluck Jr MS RRT
Ronald B George MD
James M Hurst MD
Charles G Irvin PhD
MS Jastremski MD
Robert M Kacmarek PhD RRT
Hugh S Mathewson MD
Michael McPeck BS RRT
David J Pierson MD
John Shigeoka MD
Jack Wanger MBA RPFT RRT
Jeffrey J Ward MEd RRT

JOURNAL ASSOCIATES
Stephen M Ayres MD
Reuben M Cherniack MD
Donald F Egan MD
Gareth B Gish MS RRT
George Gregory MD
Ake Grenvik MD
H Frederick Helmholz Jr MD
John E Hodgkin MD
William F Miller MD
Thomas L Petty MD
Alan K Pierce MD
Henning Pontoppidan MD
John W Severinghaus MD
Barry A Shapiro MD

PRODUCTION STAFF
Linda Barcus Donna Knauf
Steve Bowden Jeannie Marchant

CONTENTS

June 1994
Volume 39, Number 6

ORIGINAL CONTRIBUTIONS

611 A Comparison of the Imposed Work of Breathing with Endotracheal and Tracheostomy Tubes in a Lung Model
by Kenneth Davis Jr, Richard D Branson, and David Porembka—Cincinnati, Ohio

617 Evaluation of a Prototype Expiratory-Phase Aerosol Controller during Simulated Pediatric Volume-Controlled Ventilation
by Jim Keenan and John W Salyer—Salt Lake City, Utah

623 Expiratory Hold vs Clamping/Transducing for Intrinsic PEEP Determination in the Siemens 900C
by Deborah Madsen, Kelly Jager, John Fenwick, and Martin Tweeddale—Vancouver, British Columbia, Canada

CASE REPORTS

627 Bezold-Jarisch Reflex—An Indication for Closed-System Suctioning: A Case Report
by Tai-Shon Lee and Yaw Wu—Torrance, California

630 Idiopathic Vocal Cord Paralysis in a Newborn Infant: A Case Report
by Katherine A Douglas and Ramalinga Polamreddy—Toledo, Ohio

REVIEWS, OVERVIEWS, & UPDATES

635 Cerebral Gas Embolism: A Review and Update
by Vaughn Nelson, Eva Nelson, and A Joseph Layon—Gainesville, Florida

TEST YOUR RADIOLOGIC SKILL

646 Hypoxemia in a Postpartum Patient with Complex Congenital Heart Disease
by Henry Vega and Charles G Durbin Jr—Eden, North Carolina and Charlottesville, Virginia

DRUG CAPSULE

652 Drugs for Pulmonary Mycoses
by Hugh S Mathewson—Kansas City, Kansas

CLASSIC REPRINTS

657 RETROSPECTROSCOPE REDUX: "Tell It Like It Was"
by Julius H Comroe Jr (reprinted, with permission, from the American Review of Respiratory Disease 1976;113:667-676)

RESPIRATORY CARE (ISSN 00989142) is a monthly publication of Daedalus Enterprises Inc for the American Association for Respiratory Care. Copyright © 1994 by Daedalus Enterprises Inc, 11030 Ables Lane, Dallas TX 75229. All rights reserved. Reproduction in whole or in part without the express, written permission of Daedalus Enterprises Inc, is prohibited. The opinions expressed in any article or editorial are those of the author and do not necessarily reflect the views of Daedalus Enterprises Inc, the Editorial Board, or the American Association for Respiratory Care. Neither can Daedalus Enterprises Inc, the Editorial Board, or the Amercian Association for Respiratory Care be responsible for the consequences of the clinical applications of any methods or devices described herein. Printed in USA.

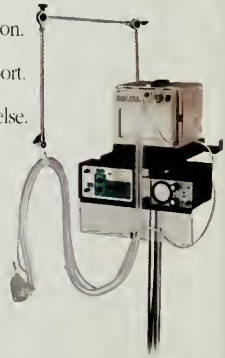
RESPIRATORY CARE is indexed in *Hospital Literature Index* and in *Cumulative Index to Nursing and Allied Health Literature.*

Subscription Rates: $5.00 per copy; $50.00 per year (12 issues) in the US; $70.00 in all other countries (add $84.00 for airmail).

Second Class Postage paid at Dallas, TX. POSTMASTER: Send address changes to RESPIRATORY CARE, Daedalus Enterprises, Inc., 11030 Ables Lane, Dallas TX 75229.

It's Getting Hard to Find Patients a BiPAP® S/T-D System Can't Help

Respironics' BiPAP S/T-D Complete Hospital System now offers ventilatory assistance to more acute care patient groups than ever. Because in addition to noninvasive ventilation, now invasive application allows support via artificial airways. The BiPAP pressure support ventilator can treat patients in the ER, the recovery room and the ICU. It's also useful during transition from invasive to noninvasive support and in weaning from mechanical ventilation. Chances are, you're thinking of someone right now who could benefit from BiPAP System support. But you may have trouble tracking down a BiPAP S/T-D System that's not already helping someone else. So call us at (800) 345-6443 and we'll help you order a BiPAP S/T-D Complete Hospital System today.



RESPIRONICS INC.®

THE FIRST NAME IN INNOVATIVE RESPIRATORY CARE

1001 Murry Ridge Drive, Murrysville, Pennsylvania 15668-8550 USA Phone (800) 345-6443 within the USA and Canada or (412) 733-0200 Fax (412) 733-0299

1993 ZENITH AWARD

WARNING: The BiPAP System is not intended to provide the total ventilatory requirements of the patient and must not be used as a life-support ventilator. Refer to the BiPAP System Clinical Manual for complete information on applications.

BiPAP is a registered trademark of Respironics Inc. BiPAP pressure support ventilators are the subject of U.S. Patents #5148802, #5239995 and other pending U.S. and foreign patents. ©Respironics Inc. 1994

Circle 116 on reader service card

MANUSCRIPT SUBMISSION

Instructions for Authors and Typists is printed near the end of RESPIRATORY CARE on a quarterly basis (Jan, Apr, July, Nov).

PHOTOCOPYING & QUOTATION

PHOTOCOPYING. Any material in this journal that is copyrighted by Daedalus Enterprises, Inc may be photocopied for noncommercial purposes of scientific or educational advancement.

QUOTATION. Anyone may, without permission, quote up to 500 words of material in this journal that is copyrighted by Daedalus Enterprises Inc, provided the quotation is for noncommercial use, and provided RESPIRATORY CARE is credited. Longer quotation requires written approval by the author and publisher.

SUBSCRIPTIONS/CHANGES OF ADDRESS

RESPIRATORY CARE
11030 Ables Lane
Dallas TX 75229-4593
(214) 243-2272

SUBSCRIPTIONS. Individual subscription rates are $50.00 per year (12 issues) in the U.S. and Puerto Rico, $70.00 per year in all other countries; $95.00 for 2 years in the U.S. and Puerto Rico, $135.00 in all other countries; and $140 for 3 years in the U.S. and Puerto Rico, $200.00 in all other countries (add $84.00 per year for air mail). Annual subscriptions are offered to members of associations according to their membership enrollment as follows: 101-500 members—$6.00, 501-1,500 members—$5.50, 1,501-10,000 members—$5.00, and over 10,000 members—$4.00. Single copies, when available, cost $5.00; add $7.00 air mail postage to overseas countries.

CHANGE OF ADDRESS. Six weeks notice is required to effect a change of address. Note your subscription number (from the mailing label) your name, and both old and new address, including zip codes. Please note your subscription number on the envelope. Copies will not be replaced without charge unless request is received within 60 days of the mailing in the U.S. or within 90 days in other countries.

MARKETING DIRECTOR

Dale Griffiths

ADVERTISING ASSISTANT

Beth Binkley

ADVERTISING. Display advertising should be arranged with the advertising representatives. RESPIRATORY CARE does not publish a classified advertising column.

PRODUCT ADVERTISING: RATES & MEDIA KITS

Aries Advertising Representatives
4 Orchard Hill Road
Marlboro NJ 07746
(908) 946-1224
fax (908) 946-1229

RECRUITMENT ADVERTISING:

Beth Binkley
RESPIRATORY CARE
11030 Ables Lane
Dallas TX 75229-4593
(214) 243-2272
fax (214) 484-6010

CONTENTS, *Continued*

June 1994
Volume 39, Number 6

BOOK REVIEWS

667 Nocturnal Asthma Mechanisms and Treatments, edited by Richard J Martin MD
reviewed by Philip Schiffman—East Brunswick, New Jersey

667 Drugs and the Lung, edited by Clive P Page PhD and W James Metzger MD, with 33 contributors
reviewed by Hugh S Mathewson—Kansas City, Kansas

668 Pulmonary Care of the Surgical Patient, edited by Leland H Hanowell MD and Forrest L Junod MD
reviewed by Philip McArdle—Charlottesville, Virginia

LETTERS

669 Administration of Air When Oxygen Was Intended
by William R Howard—Boston, Massachusetts

669 Piedalue Wants More Answers about Airway Pressure and Pulmonary Mechanics
by Fran Piedalue—Denver, Colorado; with response by David J Pierson and Jacob Hildebrandt—Seattle, Washington

671 An Addition to "Flow-Triggering Systems"
by Ray Monast—Marlborough, Massachusetts; with response by Richard D Branson—Cincinnati, Ohio

ABSTRACTS

598 Summaries of Pertinent Articles from Other Journals

NOTICES

677 Examination Dates, Notices, Prizes

CALENDAR OF EVENTS

675 Meeting Dates, Locations, Themes

MEDWATCH—PRODUCT PROBLEM REPORTING

673 Tear-Out Reporting Form

INDEXES

680 Authors in This Issue
680 Advertisers in This Issue
601 Advertiser Help Lines

Editorials and Commentaries To Note

Optimal Release Times for Airway Pressure Release Ventilation: Another Piece of the Picture—RD Cane, RA Smith. Crit Care Med 1994;22(3):397-381. (Pertains to Martin and Wetzel paper abstracted on Page 604.)

The Human Costs of Tobacco Use (second of two parts)—TD MacKenzie, CE Bartecchi, RW Schrier. N Engl J Med 1994;330(14):975.

Failure of Tuberculosis Control: A Prescription for Change (editorial)—E Bellin. JAMA 1994;271(9):708-709. (Pertains to Bloch et al paper abstracted on Page 606.)

Effect of Continuous Rotational Therapy on Intracranial Pressure in the Severely Brain-Injured Patient—JM Tillett, A Marmarou, JP Agnew, SC Choi, JD Ward. Crit Care Med 1993;21:1005.

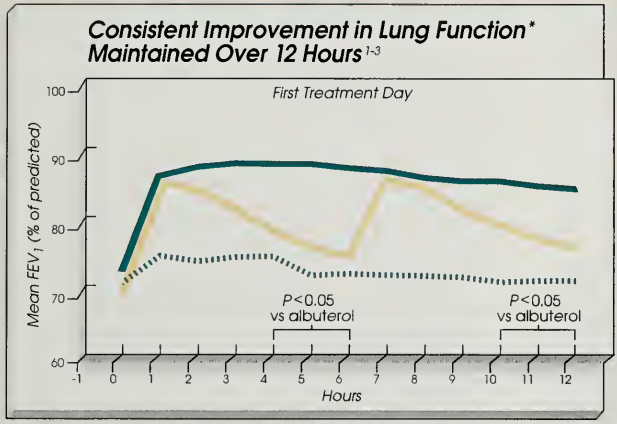
OBJECTIVE: To determine the effect of continuous rotational therapy on the dynamics of intracranial pressure. DESIGN: A controlled, prospective evaluation of intracranial pressure during continuous rotation therapy. SETTING: Neuroscience intensive care unit in a university hospital. PATIENTS: A total of 58 severely brain-injured patients (Glasgow Coma Score of ≤ 9) ranging in age from 14 to 81 yrs. INTERVENTIONS: All patients had intraventricular catheters placed to continuously monitor intracranial pressure and all patients were placed on continuous rotational therapy once stabilized. MEASUREMENTS & MAIN RESULTS: Intracranial pressure data were measured in each patient during nonrotation and these data were compared with intracranial pressure data during rotation, thus allowing each patient to serve as his own control. In addition, the intracranial pressure during rotation (40° from center) was further analyzed to determine the effect of angulation on the intracranial pressure. Analysis of computer-recorded intracranial pressure data showed no significant difference in intracranial pressure measured during rotation and nonrotation over the first 5 days postinjury. Minimal differences in intracranial pressure (< 1 to 2 mm Hg) were noted in right/center/left positions. It was also determined that intracranial pressure increased up to 6.5 mm Hg ($p = 0.12$) in patients who presented with a unilateral lesion on admission computed tomography when they rotated to the side of the lesion. However, these fluctuations did not promote additional intracranial pressure management. CONCLUSIONS: We conclude that the systemic benefits known to be derived from the use of continuous rotation therapy in the severely head-injured patient can be sustained without any deleterious effects on the intracranial pressure.

Airway Responsiveness in Young Black and White Women—CB Sherman, DJ Tollerud, LJ Heffner, FE Speizer, ST Weiss. Am Rev Respir Dis 1993;148:98.

The prevalence and severity of asthma appears to be greater in Blacks than in Whites. To determine if racial differences in airway responsiveness may explain these findings, methacholine challenge tests from 62 Black and 238 White women 20 to 35 yr of age were evaluated. Subjects served as controls for a case-control study of the relation of airway responsiveness and preterm labor. Standardized questionnaires were used to obtain information on age, obstetrical history, education, income, cigarette smoking, medication use, and respiratory illnesses and symptoms. Total serum IgE was measured using a radioimmunoassay. Methacholine challenge testing was performed on all subjects 6 wk after delivery, and the provocative dose causing a 20% decrease in FEV_1 (PD_{20}) was calculated. Black women in the study had more pregnancies and children, were younger, less well educated and more impoverished, and reported greater cigarette smoking and less medication use than did the White women. Additionally, Black women had higher geometric mean serum IgE levels (Blacks: 65.4 IU versus Whites: 20.0 IU; $p < 0.001$), lower FEV_1 (Blacks: 2.73 ± 0.38 SD L versus Whites: 3.19 ± 0.39 L; $p < 0.001$), and greater unadjusted airway responsiveness than did White women (geometric mean PD_{20}: Blacks 28.4 μmol versus Whites 38.8 μmol; $p = 0.02$). After adjusting for selective demographic

New, for asthma...

SEREVENT: The Next Dimension in Inhaled Bronchodilator Therapy



Adapted from Pearlman et al.[1]

**P<0.05 versus albuterol during the periods 4 to 6 hours after each of the two doses of albuterol. P<0.001 versus placebo throughout the 12-hour period.*

Mean FEV_1 Over 12 Hours After the First Dose of SEREVENT (Given at Hour 0 Followed by Placebo at Hour 6), Two Doses of Albuterol (Given at Hour 0 and Hour 6), and Two Doses of Placebo (Given at Hour 0 and Hour 6)

- *Proven for 12 weeks,[1,2] maintained over 12 months.[4]*
- *SEREVENT is indicated for prevention and maintenance treatment of asthma (including nocturnal asthma) in patients 12 years of age and older who require regular treatment with inhaled, short-acting β_2-agonists.*
- *Convenient twice-daily† dosing.*
- *Outstanding side effect profile comparable to albuterol.*
  - *The most common drug-related adverse events reported in clinical trials were headache (10%), tremor (3%), and cough (3%).[2]*

†Dosing should be two puffs (42 µg) of SEREVENT Inhalation Aerosol, twice daily, morning and evening, approximately 12 hours apart, for the maintenance treatment of asthma. SEREVENT should not be used for the treatment of acute exacerbations.

Please consult Brief Summary of Prescribing Information on the following pages.

New, Twice-Daily

Serevent®
(salmeterol xinafoate)
Inhalation Aerosol

Morning and Evening Inhalation for Active Days and Restful Nights

SEREVENT *60-Dose Institutional Package*	*NDC 0173-0467-00*
SEREVENT *120-Dose Trade Package*	*NDC 0173-0464-00*

Serevent®
(salmeterol xinafoate)
Inhalation Aerosol

BRIEF SUMMARY

Bronchodilator Aerosol
For Oral Inhalation Only

The following is a brief summary only. Before prescribing, see complete prescribing information in Serevent® Inhalation Aerosol product labeling.

CONTRAINDICATIONS: Serevent® Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to any of the components.

WARNINGS: 1. Not for Use to Treat Acute Symptoms; Watch for Increased Need for Short-Acting $Beta_2$-Agonists: Serevent® Inhalation Aerosol should not be used to relieve acute asthma symptoms. If the patient's short-acting, inhaled $beta_2$-agonist becomes less effective, e.g., the patient needs more inhalations than usual, medical evaluation must be obtained immediately and increasing use of Serevent Inhalation Aerosol in this situation is inappropriate. Serevent Inhalation Aerosol should not be used more frequently than twice daily (morning and evening) at the recommended dose. When prescribing Serevent Inhalation Aerosol, patients must be provided with a short-acting, inhaled $beta_2$-agonist (e.g., albuterol) for treatment of symptoms that occur despite regular twice-daily (morning and evening) use of Serevent.

Asthma may deteriorate acutely over a period of hours or chronically over several days. In this setting, increased use of inhaled, short-acting $beta_2$-agonists is a marker of destabilization of asthma and requires re-evaluation of the patient and consideration of alternative treatment regimens, especially inhaled or systemic corticosteroids. If the patient uses four or more inhalations per day of a short-acting $beta_2$-agonist on a regular basis, or if more than one canister (200 inhalations per canister) is used in an 8-week period, then the patient should see the physician for re-evaluation of treatment.

2. Use With Short-Acting $Beta_2$-Agonists: When patients begin treatment with Serevent Inhalation Aerosol, those who have been taking short-acting, inhaled $beta_2$-agonists on a regular daily basis should be advised to discontinue their regular daily-dosing regimen and should be clearly instructed to use short-acting, inhaled $beta_2$-agonists only for symptomatic relief if they develop asthma symptoms while taking Serevent Inhalation Aerosol (see PRECAUTIONS: Drug Interactions).

3. Serevent Inhalation Aerosol is Not a Substitute for Oral or Inhaled Corticosteroids: Patients must be warned not to stop or reduce corticosteroid therapy without medical advice, even if they feel better when they are being treated with Serevent.

4. Do Not Exceed Recommended Dose: As with other beta-adrenergic aerosols, Serevent Inhalation Aerosol should not be used in excess. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QT_C interval, which has the potential for producing ventricular arrhythmias.

5. Paradoxical Bronchospasm: As with other inhaled asthma medications, paradoxical bronchospasm (which can be life-threatening) has been reported following the use of Serevent Inhalation Aerosol. If it occurs, treatment with Serevent Inhalation Aerosol should be discontinued immediately and alternative therapy instituted.

6. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of Serevent Inhalation Aerosol, as demonstrated by rare cases of urticaria, rash, and bronchospasm.

PRECAUTIONS:

General: 1. Use with Spacer or Other Devices: The safety and effectiveness of Serevent® Inhalation Aerosol when used with a spacer or other devices have not been adequately studied.

2. Cardiovascular and Other Effects: No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol in recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of Serevent Inhalation Aerosol and may require discontinuation of the drug. Salmeterol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with salmeterol.

3. Metabolic Effects: Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. No effects on glucose have been seen with Serevent inhalation Aerosol at recommended doses. Administration of $beta_2$-adrenoceptor agonists may cause a decrease in serum potassium, possibly through intracellular shunting, which has the potential to increase the likelihood of arrhythmias. The decrease is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of Serevent Inhalation Aerosol at recommended doses.

Information for Patients: See illustrated Patient's Instructions for Use. **SHAKE WELL BEFORE USING.** Patients should be given the following information:

1. Not for Use to Treat Acute Symptoms: Serevent Inhalation Aerosol is not meant to relieve acute asthmatic symptoms. Acute symptoms should be treated with an inhaled, short-acting bronchodilator that has been prescribed by a physician for symptom relief.

2. Do Not Exceed Recommended Dose: The bronchodilator action of salmeterol usually lasts for at least 12 hours. Therefore it should not be used more often than every 12 hours.

3. Use With Other Medications: While using Serevent Inhalation Aerosol, other inhaled medicines should be taken only as directed by the physician.

4. Use with Short-Acting, Inhaled Beta-Agonists: While using Serevent Inhalation Aerosol, medical attention should be sought immediately if the short-acting bronchodilator treatment becomes less effective for symptom relief, if more inhalations than usual are needed, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for a 24-hour period are needed. If the patient uses four or more inhalations per day of a short-acting $beta_2$-agonist on a regular basis, or if more than one canister (200 inhalations per canister) is used in an 8-week period, then the patient should see the physician for re-evaluation of treatment.

Patients should be cautioned regarding potential adverse cardiovascular effects, such as palpitations or chest pain, related to the use of additional $beta_2$-agonist.

5. Use of Systemic or Inhaled Steroids: Serevent® (salmeterol xinafoate) Inhalation Aerosol does not replace oral or inhaled corticosteroids, the dosage of these medicines should not be changed and they should not be stopped without consulting the physician, even if the patient feels better.

6. Use for Exercise-Induced Bronchospasm: When using Serevent Inhalation Aerosol to prevent exercise-induced bronchospasm, the dose should be administered at least 30 to 60 minutes before exercise.

Drug Interactions: ***Short-Acting Beta-Agonists:*** In the two 3-month, repetitive-dose clinical trials (n=184), the mean daily need for additional $beta_2$-agonist use was 1 to 1½ inhalations per day, but some patients used more. Eight percent of patients used at least eight inhalations per day at least on one occasion. Six percent used 9 to 12 inhalations at least once. There were 15 patients (8%) who averaged over four inhalations per day. Four of these used an average of 8 to 11 inhalations per day. In these 15 patients there was no observed increase in frequency of cardiovascular adverse events. The safety of concomitant use of more than eight inhalations per day of short-acting $beta_2$-agonists with Serevent Inhalation Aerosol has not been established. In 15 patients who experienced worsening of asthma while receiving Serevent Inhalation Aerosol, nebulized albuterol (one dose in most) led to improvement in FEV_1 and no increase in occurrence of cardiovascular adverse events.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants because the action of salmeterol on the vascular system may be potentiated by these agents.

Corticosteroids and Cromoglycate: In clinical trials, inhaled corticosteroids and/or inhaled cromolyn sodium did not alter the safety profile of Serevent Inhalation Aerosol when administered concurrently.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving Serevent Inhalation Aerosol has not been completely evaluated. In one clinical trial, 87 patients receiving Serevent Inhalation Aerosol 42 mcg twice daily concurrently with a theophylline product had adverse event rates similar to those in 71 patients receiving Serevent Inhalation Aerosol without theophylline. Resting heart rates were slightly higher in the patients on theophylline but were little affected by Serevent Inhalation Aerosol therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, and leiomyomas of the uterus and a dose-related increase in the incidence of cysts in the ovaries. A higher incidence of leiomyosarcomas was not statistically significant; tumor findings were observed at oral doses of 1.4 and 10 mg/kg, which gave 9 and 63 times, respectively, the human exposure based on rodent:human AUC comparisons.

Salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts in Sprague Dawley rats in a 24-month inhalation/oral carcinogenicity study. Tumors were observed in rats receiving doses of 0.68 and 2.58 mg/kg per day (about 55 and 215 times the recommended clinical dose [mg/m^2]). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

No significant effects occurred in mice at 0.2 mg/kg (1.3 times the recommended clinical dose based on comparisons of the AUCs) and in rats at 0.21 mg/kg (15 times the recommended clinical dose on a mg/m^2 basis).

Salmeterol xinafoate produced no detectable or reproducible increases in microbial and mammalian gene mutation *in vitro*. No biastogenic activity occurred *in vitro* in human lymphocytes or *in vivo* in a rat micronucleus test. No effects on fertility were identified in male and female rats treated orally with salmeterol xinafoate at doses up to 2 mg/kg orally (about 160 times the recommended clinical dose on a mg/m^2 basis).

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** No significant effects of maternal exposure to oral salmeterol xinafoate occurred in the rat at doses up to the equivalent of about 160 times the recommended clinical dose on a mg/m² basis. Dutch rabbit fetuses exposed to salmeterol xinafoate *in utero* exhibited effects characteristically resulting from beta-adrenoceptor stimulation, these included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at 0.6 mg/kg given orally (12 times the recommended clinical dose based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at 10 mg/kg given orally (approximately 1,600 times the recommended clinical dose on a mg/m^2 basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to use in humans. There are no adequate and well-controlled studies with Serevent Inhalation Aerosol in pregnant women. Serevent Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery: There are no well-controlled human studies that have investigated effects of salmeterol on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of Serevent Inhalation Aerosol during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers: Plasma levels of salmeterol after inhaled therapeutic doses are very low (85 to 200 pg/mL) in humans. In lactating rats dosed with radiolabeled salmeterol, levels of radioactivity were similar in plasma and milk. In rats, concentrations of salmeterol in plasma and milk were similar. The xinafoate moiety is also transferred to milk in rats at concentrations of about half the corresponding level in plasma. However, since there is no experience with use of Serevent Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when salmeterol xinafoate is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of Serevent Inhalation Aerosol in children younger than 12 years of age have not been established.

Geriatric Use: Of the total number of patients who received Serevent Inhalation Aerosol in all clinical studies, 241 were 65 years and older. Geriatric patients (65 years and older) with reversible obstructive airway disease were evaluated in four well-controlled studies of 3 weeks' to 3 months' duration. Two placebo-controlled, crossover studies evaluated twice-daily dosing with salmeterol for 21 to 28 days in 45 patients. An additional 75 geriatric patients were treated with salmeterol for 3 months in two large parallel-group, multicenter studies. These 120 patients experienced increases in AM and PM peak expiratory flow rate and decreases in diurnal variation in peak expiratory flow rate similar to responses seen in the total populations of the two latter studies. The adverse event type and frequency in geriatric patients were not different from those of the total populations studied.

No apparent differences in the efficacy and safety of Serevent Inhalation Aerosol were observed when geriatric patients were compared with younger patients in clinical trials. As with other $beta_2$-agonists, however, special caution should be observed when using Serevent Inhalation Aerosol in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Based on available data, no adjustment of salmeterol dosage in geriatric patients is warranted.

Serevent® (salmeterol xinafoate) Inhalation Aerosol

ADVERSE REACTIONS: Adverse reactions to salmeterol are similar in nature to reactions to other selective beta$_2$-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, rash, bronchospasm (see WARNINGS); headache; tremor; nervousness; and paradoxical bronchospasm (see WARNINGS).

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of Serevent® (salmeterol xinafoate) Inhalation Aerosol in patients 12 years of age and older with asthma. The following table reports the incidence of adverse events in these two studies.

Adverse Experience Incidence in Two Large 12-Week Clinical Trials*

Adverse Event Type	Percent of Patients		
	Placebo n=187	Serevent 42 mcg b.i.d. n=184	Albuterol 180 mcg q.i.d. n=185
Ear, nose, and throat			
Upper respiratory tract infection	13	14	16*
Nasopharyngitis	12	14	11
Disease of nasal cavity/sinus	4	6	1
Sinus headache	2	4	<1
Gastrointestinal			
Stomachache	0	4	0
Neurological			
Headache	23	28	27
Tremor	2	4	3
Respiratory			
Cough	6	7	3
Lower respiratory infection	2	4	2

* The only adverse experience classified as serious was one case of upper respiratory tract infection in a patient treated with albuterol.

The table above includes all events (whether considered drug related or nondrug related by the investigator) that occurred at a rate of over 3% in the Serevent Inhalation Aerosol treatment group and were more common in the Serevent Inhalation Aerosol group than in the placebo group.

Pharyngitis, allergic rhinitis, dizziness/giddiness, and influenza occurred at 3% or more but were equally common on placebo. Other events occurring in the Serevent inhalation Aerosol treatment group at a frequency of 1% to 3% were as follows:

Cardiovascular: Tachycardia, palpitations.
Ear, Nose, and Throat: Rhinitis, laryngitis.
Gastrointestinal: Nausea, viral gastroenteritis, nausea and vomiting, diarrhea, abdominal pain.
Hypersensitivity: Urticaria.
Mouth and Teeth: Dental pain.
Musculoskeletal: Pain in joint, back pain, muscle cramp/contraction, myalgia/myositis, muscular soreness.
Neurological: Nervousness, malaise/fatigue.
Respiratory: Tracheitis/bronchitis.
Skin: Rash/skin eruption.
Urogenital: Dysmenorrhea

In small dose-response studies, tremor, nervousness, and palpitations appeared to be dose related.

OVERDOSAGE: Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to clinically significant prolongation of the QT_c interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

In these cases, therapy with Serevent® Inhalation Aerosol and all beta-adrenergic–stimulant drugs should be stopped, supportive therapy provided, and judicious use of a beta-adrenergic blocking agent should be considered, bearing in mind the possibility that such agents can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

As with all sympathomimetic pressurized aerosol medications, cardiac arrest and even death may be associated with abuse of Serevent Inhalation Aerosol.

Rats and dogs survived the maximum practicable inhalation doses of salmeterol of 2.9 and 0.7 mg/kg, respectively. The maximum nonlethal oral doses in mice and rats were approximately 150 mg/kg and >1,000 mg/kg, respectively.

Dialysis is not appropriate treatment for overdosage of Serevent Inhalation Aerosol.

Allen & Hanburys
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

February 1994
RL-096

References:

1. *Pearlman DS, Chervinsky P, LaForce C, et al. A comparison of salmeterol with albuterol in the treatment of mild-to-moderate asthma.* N Engl J Med. *November 1992;327:1420-1425.* ***2.*** *Data on file, Glaxo Inc.* ***3.*** *Ullman A, Svedmyr N. Salmeterol, a new long acting inhaled β_2 adrenoceptor agonist: comparison with salbutamol in adult asthmatic patients.* Thorax. *1988;43:674-678.* ***4.*** *Britton MG, Earnshaw JS, Palmer JBD. A twelve month comparison of salmeterol with salbutamol in asthmatic patients.* Eur Respir J. *1992;5:1062-1067.*

For more information, contact your Allen & Hanburys sales representative.

Allen & Hanburys
DIVISION OF GLAXO INC.
a world leader in respiratory care
Research Triangle Park, NC 27709

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.

SER094R0 Printed in USA March 1994

Circle 142 on reader service card

For your convenience, and direct access, the advertisers in this issue and their phone numbers are listed below. Please use this directory for requesting written material or for any question you may have.

HELP LINES

AARC Information	214-243-2272
Allen & Hanburys Div of Glaxo Inc	919-248-2100
CNS Inc	800-843-2978
DHD Diemolding Healthcare Div	800-847-8000
Dräger Critical Care Systems	703-817-0100
HealthScan Products Inc	800-962-1266
HR Inc	800-426-1042
Monaghan Medical Products Corp	800-833-9653
Respironics Inc	800-345-6443
Sherwood Medical	800-325-7472
Siemens Medical Systems	800-333-8646

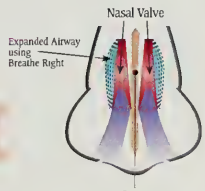
Breathe Right™

Dramatic 31% Reduction in Nasal Airway Resistance.

Considering that the nose accounts for 50% of total airway resistance, why not improve air flow easily and without medicinal side-effects.

Instant relief from nasal congestion and dryness associated with conditions such as CPAP treatment, oxygen administration and allergies.

- Drug-free, no adverse effects from long term use.
- Ideal for night-time use.



To Order Call
800-843-2978

CNS®
1250 Park Road
Chanhassen, MN 55317-9260

© 94
Breathe Right is a trademark of CNS, Inc.
U.S. and Foreign Patents Pending.

Circle 144 on reader service card

and smoking differences, a significant additional effect of race on mean PD_{20} was found. However, after adjustment for level of serum IgE and level of FEV_1, racial differences were no longer apparent. Similar results were found when asthmatics were excluded from the analyses (Black asthmatics, n = 6: 9.7% versus White asthmatics, n = 19: 8.0%) and when only subjects with heightened airway responsiveness were included in the analyses (Blacks, n = 21: 33.9% versus Whites, n = 45: 18.9%). These findings suggest that young Black women have a greater degree of methacholine airway responsiveness than do White women of comparable age. Higher levels of serum IgE and lower levels of lung function in Blacks may explain these findings.

Cognitive Function and Spirometry Performance in the Elderly—CB Sherman, D Kern, ER Richardson, M Hubert, BS Fogel. Am Rev Respir Dis 1993;148:123.

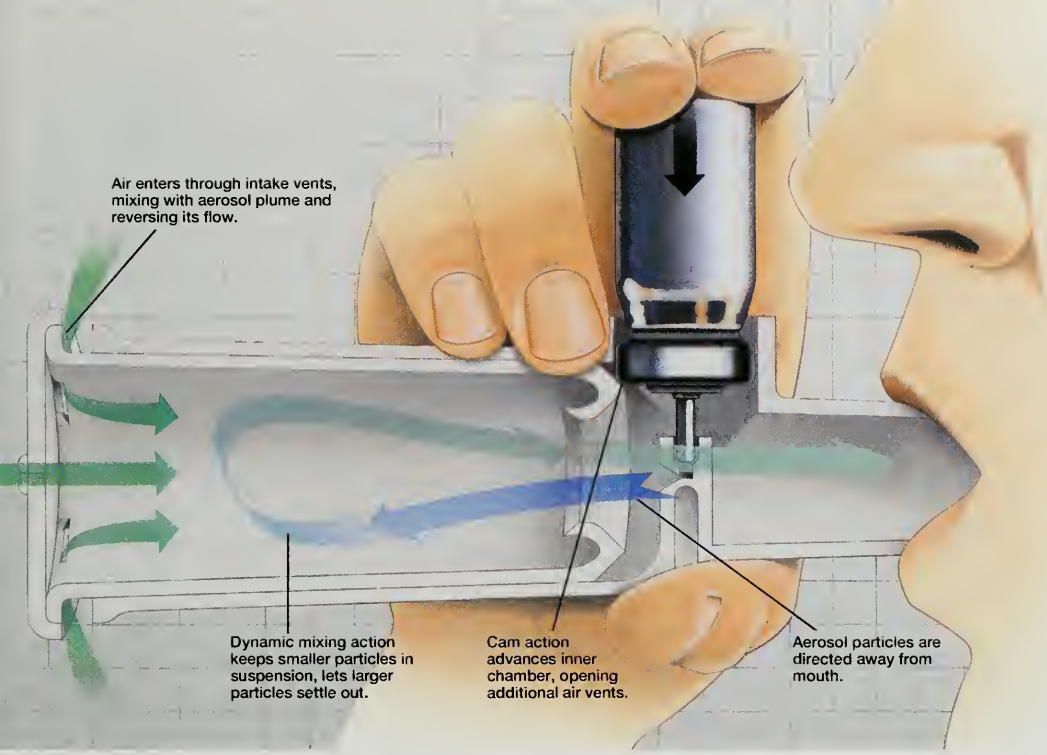
A total of 65 ambulatory subjects over the age of 65 yr were studied to determine if mild impairment in cognitive function precludes reliable spirometric measures in the aged. Standardized questionnaires were used to obtain information on demographics, cigarette smoking, respiratory symptoms, and physician-diagnosed lung disease. Each subject performed several simple standardized tasks of cognitive function and underwent spirometric testing. A total of 36 women and 29 men participated. The mean age for the group was 74.9 ± 5.6 yr; most were nonsmokers (never smokers, n = 28; former smokers, n = 29; and current smokers, n = 8). Of the 65 participants, 8 (12.3%) individuals were unable to perform at least 3 ATS-acceptable FVC maneuvers after suitable demonstration. These subjects were similar to the 57 subjects able to perform 3 acceptable maneuvers, except for worse scores on both the symbol-digit modalities test (23.3 ± 3.6 versus 31.6 ± 10.5, $p < 0.001$) and the trail-making test, Part B (244.3 ± 87.1 versus 160.4 ± 71.8, $p < 0.01$). Of the 57 subjects able to perform spirometry, 18 (31.6%) failed to meet ATS reproducibility criteria for FEV_1, FVC, or both. Cognitive impairment was not associated with the ability to achieve reproducible measures. These results suggest that the vast majority of older subjects can perform reliable spirometry; those elderly unable to perform spirometry may have impairment in cognitive function requiring further evaluation.

Oxygen Consumption and Resting Metabolic Rate in Sepsis, Sepsis Syndrome, and Septic Shock—G Kreymann, S Grosser, P Buggisch, C Gottschall, S Matthaei, H Greten. Crit Care Med 1993;21:1012.

OBJECTIVE: To test the hypothesis that variations in oxygen consumption ($\dot{V}_{O_2}$) and resting metabolic rate reflect the severity of bacterial infections and reflect the development of sepsis syndrome and septic shock. DESIGN: Observational study with sequential measurements of $\dot{V}_{O_2}$ and resting metabolic rate by expiratory gas analysis. SETTING: Medical intensive care unit. PATIENTS: Thirty patients, treated primarily for presumed bacterial infection, were examined on 118 treatment days. INTERVENTIONS: None. MEASUREMENTS & MAIN RESULTS: $\dot{V}_{O_2}$ and resting metabolic rate were measured by expiratory gas analysis. For mechanically ventilated patients, a measurement system was developed, based on a paramagnetic oxygen sensor, an infrared CO_2 sensor, and digital signal averaging. Measurements in spontaneously breathing patients were performed with a metabolic monitor. Patients were assigned by clinical criteria to the following groups: sepsis, sepsis syndrome, and septic shock. The lowest $\dot{V}_{O_2}$ value of each patient in each stage was evaluated. Mean $\dot{V}_{O_2}$ in 15 patients with sepsis was 180 ± 19 (SD) mL/min/m^2, in 11 patients with sepsis syndrome 156 ± 22 mL/min/m^2, and in eight patients with septic shock 120 ± 27 mL/min/m^2 ($p < 0.001$). Mean resting metabolic rate in sepsis was +55 ± 14%, in sepsis syndrome +24 ± 12%, and in septic shock +2 ± 24% ($p < 0.001$). Mean oxygen delivery ($\dot{D}_{O_2}$) was 501 ± 116 mL/min/m^2 in sepsis, 515 ± 186 mL/min/m^2 in sepsis syndrome, and 404 ± 96 mL/min/m^2 in septic shock. Oxygen extraction ($\dot{V}_{O_2}/\dot{D}_{O_2}$) was highest in sepsis (0.39 vs 0.33 in sepsis syndrome and 0.29 in septic shock). During recovery from sepsis syndrome or septic shock, a significant increase in resting metabolic rate to +61 ± 22% was measured in nine patients. CONCLUSIONS: In sepsis syndrome, $\dot{V}_{O_2}$ and resting metabolic rate are enhanced by 30% compared with normal basal metabolism, but they are markedly reduced compared with uncomplicated sepsis. The higher $\dot{V}_{O_2}$ in uncomplicated sepsis is flow independent. The noninvasive measurement of $\dot{V}_{O_2}$ and resting metabolic rate by expiratory gas analysis therefore can be used as a quantitative staging and monitoring parameter for the development of sepsis syndrome and septic shock.

Positive End-Expiratory Pressure-Induced, Calcium-Channel-Mediated Increases in Pulmonary Vascular Resistance in Neonatal Lambs—ST Venkataraman, BP Fuhrman, DF Howland, M DeFrancisis. Crit Care Med 1993; 21:1066.

OBJECTIVES: (a) To study the dose response of the calcium-channel-mediated increases in pulmonary vascular resistance with different levels of positive end-expiratory pressure; (b) to study the reversibility of the calci-


Air enters through intake vents, mixing with aerosol plume and reversing its flow.
Dynamic mixing action keeps smaller particles in suspension, lets larger particles settle out.
Cam action advances inner chamber, opening additional air vents.
Aerosol particles are directed away from mouth.

Anatomy of a Breakthrough

OptiHaler® reinvents MDI delivery.

Its patented aerodynamic design creates a more effective aerosol mixture — and makes more of that mixture available for delivery to the lungs — than ordinary static spacers.[1]

True Portability
OptiHaler goes anywhere...and the MDI canister stores inside.

All in a convenient, compact unit as easy to use as **1,2,3.**

1. Patient begins inhaling.

2. Patient presses and holds down MDI canister, continuing to take a full, deep breath.

3. Patient holds breath for 8–10 seconds.

Give your patients the full benefit of their MDI medication. Recommend OptiHaler.

Reference 1 Data on file, HealthScan Products Inc U S Patent No 5,040,527 0A760003-0 4/93

To see how your patients can benefit from OptiHaler, call **1-800-962-1266** or use this coupon.

OptiHaler®

Drug Delivery System For Use With Metered Dose Inhalers
The promise of MDI therapy...delivered.
From the makers of ASSESS® & Personal Best™ Peak Flow Meters

Name_____
Institution_____
Address_____
City_____ State_____ ZIP_____
Telephone ( )_____

RC/06/94

HealthScan Products Inc.
908 Pompton Avenue
Cedar Grove, NJ 07009-1292

Circle 120 on reader service card

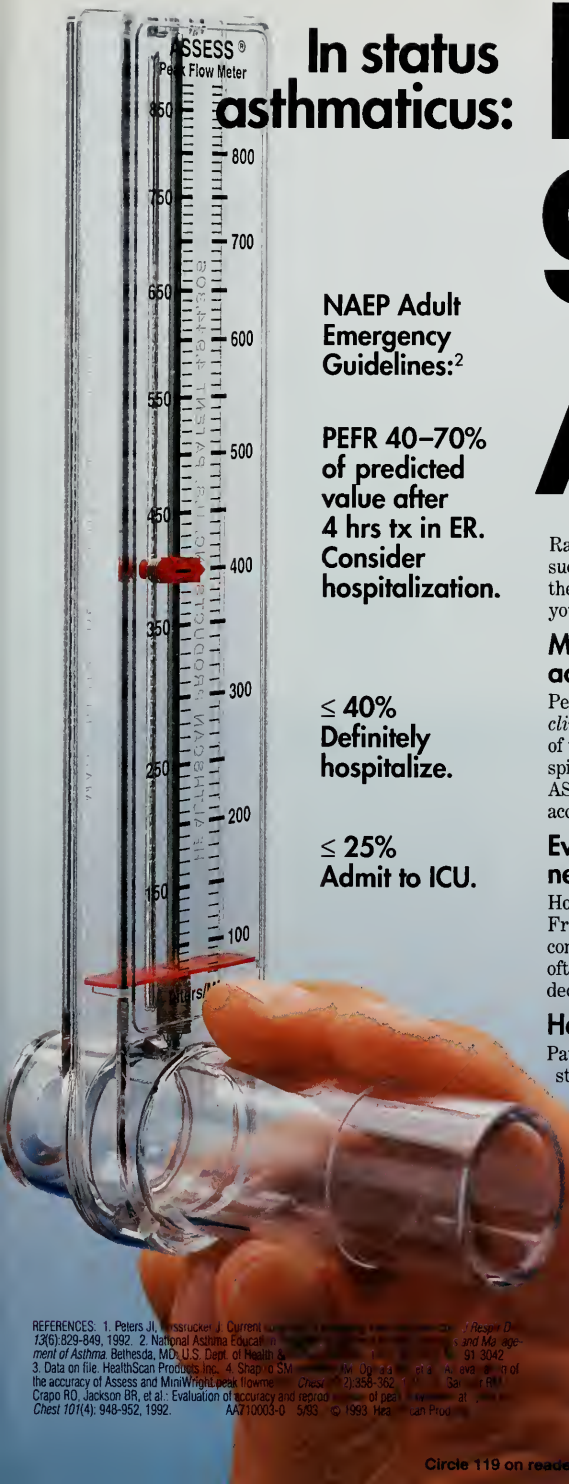
um-channel mediated increases in pulmonary vascular resistance after discontinuation of positive end-expiratory pressure; and (c) to study the effect of cyclooxygenase and lipoxygenase inhibition on the calcium-channel mediated increases in pulmonary vascular resistance. DESIGN: A prospective, multiexperimental, dose response study. SETTING: Laboratory setting in a university hospital. SUBJECTS: Twenty-three 4- to 10-day-old neonatal lambs. INTERVENTIONS & MEASUREMENTS: Lungs of neonatal lambs were isolated in situ, perfused at a constant flowrate, and ventilated at a fixed tidal volume and rate. Mean pulmonary arterial pressure responses to the application and discontinuation of four levels (3.7, 7.4, 11, and 14.7 mm Hg) of positive end-expiratory pressure were studied before and after calcium-channel blockade with verapamil (5 mg) (n = 12). In addition, the mean pulmonary arterial pressure response to 11 mm Hg of positive end-expiratory pressure was studied before and after inhibition of cyclooxygenase with indomethacin (10 mg/kg) (n = 6) and lipoxygenase with diethylcarbamazine (100 mg/kg) (n = 5). RESULTS: The magnitude of the calcium-channel-dependent mean pulmonary arterial pressure response 4 mins after the application of positive end-expiratory pressure was dose related (2.1, 3.0, 4.1, and 5.5 mm Hg with 3.7, 7.4, 11.0, and 14.7 mmHg positive end-expiratory pressure, respectively) and entirely reversible on discontinuation of positive end-expiratory pressure with a time course of 2 to 4 mins. Neither indomethacin nor diethylcarbamazine affected the pulmonary arterial pressure responses to positive end-expiratory pressure. Airway pressure changes with positive end-expiratory pressure were not affected by verapamil, indomethacin, or diethylcarbamazine. CONCLUSIONS: The calcium-channel-mediated pulmonary arterial pressure responses with positive end-expiratory pressure, applied during continuous positive pressure breathing, occur even at low levels of positive end-expiratory pressure, are dose dependent, and are not abolished by treatment with indomethacin or diethylcarbamazine.

High-Compliance Tuberculosis Treatment Programme in a Rural Community—D Wikinson. Lancet 1994;343:647.

The global tuberculosis epidemic is being fueled by dual infection with human immunodeficiency virus type 1. Shortcourse chemotherapy is effective but usually fails for operational reasons. A community-based treatment programme of twice-weekly fully-supervised treatment is described in which 89% of surviving patients completed treatment under programme conditions. Half the patients were successfully supervised by non-health workers. New approaches are needed to combat the global tuberculosis epidemic.

Optimal Release Time during Airway Pressure Release Ventilation in Neonatal Sheep—LD Martin, RC Wetzel. Crit Care Med 1994;22(3):486.

OBJECTIVE: To systematically investigate the effect of altering release time during airway pressure release ventilation in a neonatal animal model before and after oleic acid-induced acute lung injury. DESIGN: Prospective, nonrandomized, controlled study with repeated measures. SETTING: University research laboratory. SUBJECTS: Eight neonatal sheep (aged < 7 days, weight 5.1 ± 0.3 kg). INTERVENTIONS: Throughout this study, airway pressure release ventilation was performed with an F_{IO_2} of 0.21 at a frequency of 0.5 Hz (30 breaths/min) and an airway plateau pressure set to deliver tidal volumes between 10 and 15 mL/kg with a release time of 1 second. Release time was changed in decrements of 0.2 second starting at 1 second and ending at 0.2 second at 10-min intervals. Cardiorespiratory profiles were recorded at the end of each interval. The total exhaled respiratory system time constant (τ) was measured by plotting exhaled volume (integration of exhaled airflow) vs time. Acute lung injury was induced by oleic acid infusion. The protocol was repeated with increased plateau airway pressure to maintain tidal volumes between 10 and 15 mL/kg at a release time of 1 second. MEASUREMENTS & MAIN RESULTS: During airway pressure release ventilation at a release time of 1 second, oleic acid-induced acute lung injury decreased dynamic lung compliance (9.9 ± 2.2 vs 7.5 ± 2.0 mL/cm H_2O, $p < 0.01$), the expiratory time constant (0.15 ± 0.04 vs 0.12 ± 0.02 second, $p < 0.05$), and mean arterial pressure (80 ± 5 vs 62 ± 12 mm Hg, $p < 0.01$). Alveolar ventilation was maintained as long as release times were > 0.4 second ($\approx 3\tau$ or greater). P_{aO_2} decreased with release times of < 0.3 second, but the alveolar-arterial oxygen tension difference was unchanged. In this protocol, with higher plateau and mean airway pressures, oleic acid-induced acute lung injury had no effect on the relationship between release time and oxygenation or ventilation. CONCLUSIONS: In this neonatal laboratory model, release times that were much shorter than previously reported maintained clinically acceptable oxygenation and ventilation. The optimal duration of the release time is a function of the time constant of the respiratory system. During airway pressure release ventilation, alveolar ventilation was maintained without apparent lung volume loss with release times of between 4τ and 10τ.



In status asthmaticus:

Don't guess.

Assess.

NAEP Adult Emergency Guidelines:[2]

PEFR 40–70% of predicted value after 4 hrs tx in ER. Consider hospitalization.

≤ 40% Definitely hospitalize.

≤ 25% Admit to ICU.

Rapid initiation and close monitoring of therapy are vital to successful ER management of severe asthma.[1] That's why the ASSESS® Peak Flow Meter should be a vital part of your armamentarium. ASSESS lets you —

Measure airway obstruction easily, accurately, cost-effectively.

Peak expiratory flow rate (PEFR) provides an objective, *clinically relevant* measurement of airflow — at a fraction of the cost, bulk, and inconvenience of conventional spirometry.[2] And when seconds count, you can count on ASSESS to deliver those measurements with superior accuracy and reproducibility.[3-5]

Evaluate response to therapy and need for hospitalization.

How is your patient doing? What should *you* be doing? From initial presentation through discharge, the rugged, compact ASSESS gives you the hard data you need — as often as you need it — to help you make informed treatment decisions in line with NAEP recommendations.[2]

Help prevent future acute exacerbations.

Patients don't come back when their maintenance therapy stays on track. Keep it on track with ASSESS — and a regular program of PEFR monitoring at home, work, or school — as a routine part of your discharge orders.

For more information about how ASSESS can help you deliver better asthma care, **call HealthScan Products at 1-800-962-1266.**

ASSESS® Peak Flow Meter

STANDARD RANGE 60 to 880 L/min

LOW RANGE 30 to 390 L/min

Setting the standard for peak flow monitoring.

REFERENCES. 1. Peters JI, Strosucker J. Current [illegible] *Respir Dis* 13(6):829-849, 1992. 2. National Asthma Education [illegible] *and Management of Asthma*. Bethesda, MD: U.S. Dept. of Health & [illegible] 91 3042 3. Data on file. HealthScan Products Inc. 4. Shapiro SM. [illegible] Evaluation of the accuracy of Assess and MiniWright peak flowmeters. *Chest* 97(2):358-362, [illegible] Santiago RM, Crapo RO, Jackson BR, et al.: Evaluation of accuracy and reproducibility of peak [illegible] at [illegible] *Chest 101*(4): 948-952, 1992.

AA710003-0 5/93 © 1993 Healthscan Products

Circle 119 on reader service card

Nationwide Survey of Drug-Resistant Tuberculosis in the United States—AB Bloch, GM Cauthen, IM Onorato, KG Dansbury, GD Kelly, CR Driver, DE Snider Jr. JAMA 1994;271(9):665.

OBJECTIVE: To determine antituberculosis drug resistance patterns, geographic distribution, demographic characteristics, and risk factors of reported tuberculosis (TB) patients in the United States. DESIGN: Survey of reported TB cases in the United States. For culture-positive cases reported to the Centers for Disease Control and Prevention, we asked health departments to provide drug susceptibility test results from initial *Mycobacterium tuberculosis* isolates. STUDY POPULATION: Culture-positive TB cases in the United States reported during the first quarter of 1991. MAIN OUTCOME MEASURES: Individual TB case reports submitted to the Centers for Disease Control and Prevention and drug susceptibility test results. RESULTS: Resistance to one or more antituberculosis drugs was found in 14.2% of cases. Resistance to isoniazid and/or rifampin was found in 9.5% of cases whose isolates were tested against one or both drugs, such cases were found in 107 counties in 33 states. Resistance to both isoniazid and rifampin (multidrug-resistant [MDR] TB) was found in 3.5% of cases whose isolates were tested against both drugs; such cases were found in 35 counties in 13 states. New York City accounted for 61.4% of the nation's MDR TB cases. The 3-month population-based incidence rate of MDR TB in New York City was 52.4 times (95% confidence interval [CI] 35.5 to 78.3) that of the rest of the nation (9.559 vs 0.182 cases per million population). Compared with the rate in non-Hispanic Whites in the rest of the nation (0.032 cases per million), the relative risk of MDR TB in New York City non-Hispanic Whites was 39.0 (95% CI 8.1 to 164.5), 299.3 (95% CI 112.5 to 927.1) in Hispanics, 420.9 (95% CI 121.0 to 1515.8) in Asian/Pacific Islanders, and 701.0 (95% CI, 296.4 to 2018.1) in non-Hispanic Blacks. CONCLUSIONS: With nearly 10% of TB patients resistant to isoniazid and/or rifampin, greater use of four-drug regimens and directly observed therapy is indicated. Aggressive intervention to prevent the further spread of MDR TB is needed to find every TB patient and

Your Staff Earns Continuing Education Credit Without Even Leaving Your Facility

Professor's Rounds in Respiratory Care

Part IV: Blood Gas and Related Measurements: Laboratory Versus Bedside Devices
(One CE Credit)
July 26: 12:30 p.m. to 2:00 p.m.
Eastern Time

Part V: Hospital Operational Restructuring and Respiratory Care
(One CE Credit)
September 13: 12:30 p.m. to 2:00 p.m.
Eastern Time

Part VI: The New Ventilator Management: Permissive Hypercapnia and other Variations on Conventional Mechanical Ventilation
(One CE Credit)
November 8: 12:30 p.m. to 2:00 p.m.
Eastern Time

$250 Each for AARC Members
$285 Each for Nonmembers
Call Now to Start Earning CE Credit
(214) 830-0061

A Continuing Education Program of the American Association for Respiratory Care

Baxter
Supported in part by an educational grant from Baxter Healthcare Corporation I.V. Systems Division

A VHA Satellite Network Production

EVERYONE'S CONCERN!
MEDICAL COSTS • MEDICAL WASTE • PERSONNEL SAFETY
Think Globally, Act Locally
Think Pasteurization, Think HR

Steri-Vers Washer Plus

The Steri-Vers System and Washer Plus wash and pasteurize better with agitation!
NO DRIP!
NO FUSS!
NO MUSCLE!

Choose the Best!
Efficient! Insulated!
Warm Inside - Cool Outside
Aerotherm Dryer

Aerosol Treatment Guard

Reduce exposure to TB. Safety and peace of mind with the ATG!

HR Incorporated
P.O. Box 1744 • Bellevue, WA 98009 • (800) 426-1042 • Fax (206) 881-3654

Circle 106 on reader service card

to provide optimal patient management to ensure completion of chemotherapy.

Outcome of Out-of-Hospital Cardiac Arrest in New York City: The Pre-Hospital Arrest Survival Evaluation (PHASE) Study—G Lombardi, EJ Gallagher, P Gennis. JAMA 1994; 271:678.

OBJECTIVE: To determine survival from out-of-hospital cardiac arrest in New York City and to compare this with other urban, suburban, and rural areas. DESIGN: Observational cohort study. SETTING: New York City. PARTICIPANTS: Consecutive out-of-hospital cardiac arrests occurring between October 1, 1990, and April 1, 1991. INTERVENTION: Trained paramedics performed immediate postarrest interviews with care providers, using a standardized questionnaire. MAIN OUTCOME MEASURES: Entry criteria, elapsed time intervals, and nodal events conformed to Utstein recommendations. The single target endpoint was death or discharge home. RESULTS: Of 3,243 consecutive cardiac arrests on which resuscitation was attempted, 2,329 (72%) met entry criteria as primary cardiac events. Overall survival was 1.4% (99% confidence interval [CI] 0.9% to 2.3%). No patients were lost to follow-up. Survival from witnessed ventricular fibrillation was 5.3% (99% CI 2.9% to 8.8%). Using survival from witnessed ventricular fibrillation for intersystem comparison, our survival rate was similar to that of Chicago IL (4.0%; 99% CI, 1.9% to 7.5%; $p = 0.41$), the only other large city on which data were available. However, it was significantly lower than that reported from midsized urban/suburban areas (33.0%; 99% CI 30.4% to 35.6%; $p < 0.0001$) and suburban/rural areas (12.6%; 99% CI 8.9% to 16.3%; $p < 0.0001$). Survival rate among arrests occurring after arrival of emergency medical services personnel (8.5%; 99% CI 4.7% to 14.0%) was comparable with Chicago (6.6%; 99% CI 3.3% to 11.5%; $p = 0.41$) but markedly lower than King County, Washington (36%; 99% CI 28.6% to 43.8%; $p < 0.0001$). CONCLUSIONS: Survival from out-of-hospital cardiac arrest in New York City was poor. This was partly attributable to lengthy elapsed time intervals at every step in the chain of survival. However, examination of survival among arrests occurring after emergency medical services arrival suggests that other features may predispose residents of large cities to higher cardiac arrest mortality than individuals living in more suburban or rural settings. Since half the U.S. population resides in large metropolitan areas, this represents a public health problem of considerable magnitude.

Coming in the August Issue

CRCE through the Journal

6 hours of CRCE credit for reading RESPIRATORY CARE

AN INNOVATIVE SOLUTION

The New TruZone™ Peak Flow Meter
True Versatility!

Monaghan Medical Corporation
manufacturers of the AeroChamber® Family of Aerosol Holding Chambers.

For more information, call or write:
Monaghan Medical Corporation, PO Box 2805, Plattsburgh, NY 12901-0299
TruZone™ PFM Customer Service 1-800-833-9653 EXT # 208

IN PEAK FLOW MONITORING

Peak Flow Meter

TRU PFM ZONE™

Logarithmic Scale
Simplifies reading of Peak Expiratory Flow Rate (PEFR)

One unit satisfies the standards for both children and adults

Cost Effective
One peak flow meter for all users

One peak flow meter for asthma or emphysema patients

ColorZone™ Tapes
True zones as suggested by the NAEP

Actual zones, not end points, are easily identified

Facilitates customization as suggested by NAEP

ColorZones™ are transparent – indicator is easy to see

Internal Indicator
Reliable and accurate readings – indicator is enclosed and tamper proof

Transparent body of the TruZone™ can be held in any manner

Prevents inadvertent changes to the PEFR readings

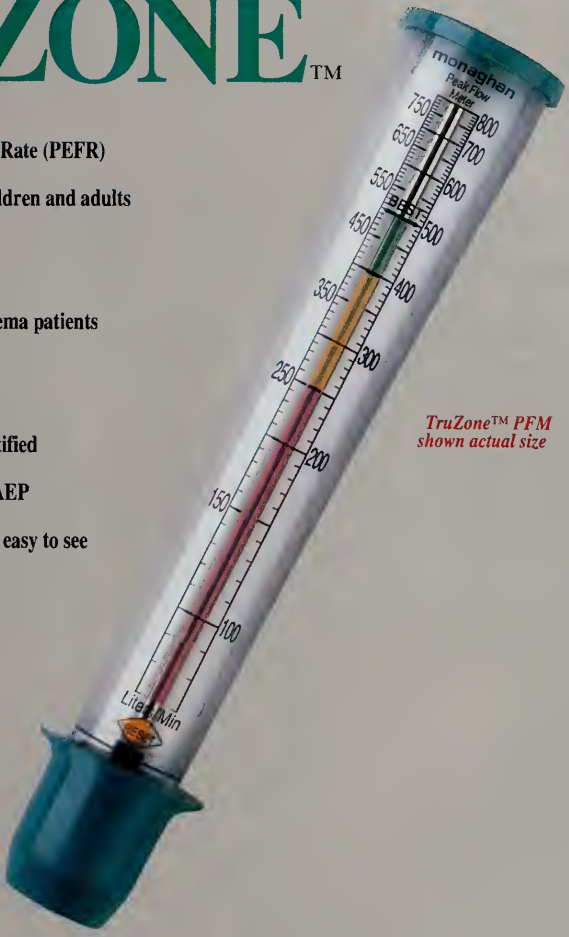
User friendly – facilitates patient compliance

Unique Body Shape
Comfortable to hold

Ready for convenient use at all times

Nothing to unfold or assemble

Fits in pocket or purse



TruZone™ PFM shown actual size

The TruZone™ PFM meets all NAEP standards.

monaghan

Peak Performance U.S.A.
Sponsors of AARC'S Peak Performance USA Program

AARC ZENITH AWARD 1993

Circle 124 on reader service card

PRESENTING THE FIRST PORTABLE VENTILATOR THAT DOESN'T HAVE TO APOLOGIZE FOR BEING PORTABLE!

Compare Uni-Vent™ to any other portable ventilator and you will quickly see why the Model 750 is in a class by itself.*

*Respiratory Care Magazine, January 1992, Vol. 37, No. 1.

- Control, Assist-Control and SIMV operating modes, optional electronic demand valve - all PEEP compensable!
- Comprehensive alarm system and automatic continuous system self-checks for maximum safety!
- Easy-to-operate, logical control groupings, simplify personnel training!
- Operates from internal battery or external power - consumes no gas!
- High-reliability, electronic circuitry is unaffected by changes in altitude!

For more information on the Uni-Vent™ Model 750, or the name of your local Representative, call Impact today!
IMPACT Instrumentation, Inc., 27 Fairfield Place, P.O. Box 508, West Caldwell, NJ 07006 1-800/969-0750

Circle 96 on reader service card

A Comparison of the Imposed Work of Breathing with Endotracheal and Tracheostomy Tubes in a Lung Model

Kenneth Davis Jr MD, Richard D Branson RRT, and David Porembka DO

BACKGROUND: Artificial airways have been shown to increase flow resistance and the work of breathing (WOB) as inside diameters decrease and inspiratory flow increases. PURPOSE: We designed a study to evaluate the imposed work of breathing (WOB_I) in a lung model, using both endotracheal (ETT) and tracheostomy tubes (TT). We hypothesized that the shorter, more rigid TT might result in a lower WOB_I than that imposed by a thermolabile ETT of the same size. MATERIALS & METHODS: A patient model was created using an intubation mannequin, simulated trachea, and two-chamber test lung. One side of the test lung was connected to a ventilator to simulate spontaneous breathing. The ventilator was set to deliver a V_T of 500 mL at flows of 0.5, 1.0, and 1.5 L/s. ETT with inside diameters (ID) of 6.0-, 7.0-, 8.0-, and 8.5-mm ID and TT with ID of 5.0-, 7.0-, 8.5-, and 9.0-mm ID were placed in the model. WOB_I was measured by a VenTrak respiratory monitor. A pneumotachograph and pressure tap were placed at the proximal airway and a second pressure tap was located below the distal tip of the artificial airway. WOB and peak negative pressure (PNP) were recorded from the average of 10 breaths at each flow setting. RESULTS: WOB_I and PNP varied inversely with ID and directly with inspiratory flow. With each increase in flow, both WOB_I and PNP increased ($p < 0.01$) for each tube. For equivalent ID, 7.0- and 8.5-mm ID ETTs had significantly higher PNP and WOB_I at 1.0 L/s ($p < 0.05$) and 1.5 L/s ($p < 0.01$) than did 7.0- and 8.5-mm TTs. CONCLUSION: The WOB_I of artificial airways increases with decreasing ID, increasing length, and increased patient demand. For identical ID, the shorter, more rigid TT results in a lower WOB_I and PNP than equivalently sized ETT. Clinicians should be aware of the contribution of artificial airways to WOB_I and select the appropriate airway for patients. [Respir Care 1994;39(6):611-616.]

Background and Study Purpose

Several authors have measured the contribution of artificial airways on the imposed work of breathing (WOB_I).[1-7] Under conditions of constant, laminar flow, the resistance of an artificial airway is directly proportional to the length and inversely proportional to the fourth power of the internal radius.[8] However, Wright et al[3] have shown that in-vivo endotracheal tube (ETT) resistance is grossly underestimated from in-vitro data.

The presence of a small-lumen artificial airway can increase the work of breathing, contribute to development of auto-PEEP, precipitate respiratory muscle fatigue, and preclude weaning.[1,2] The resistance of artificial airways also needs to be accounted for during measurements of respiratory mechanics.[8]

We have observed patients who having failed repeated weaning attempts return from the operating

Dr Davis is Associate Professor of Surgery and Anesthesia, Mr Branson is Assistant Professor of Clinical Surgery, and Dr Porembka is Associate Professor of Anesthesia—University of Cincinnati Medical Center, Cincinnati, Ohio.

None of the authors has any financial interest in any of the products used or evaluated.

Reprints: Richard D Branson RRT, Dept of Surgery ML 558, University of Cincinnati Medical Center, 231 Bethesda Ave, Cincinnati OH 45267-0558.

room following tracheostomy without further need for mechanical ventilation. This observation resulted in the speculation that tracheostomy tubes (TT) may impose a lower WOB_I than ETT, secondary to their rigidity and shorter length. A literature search failed to demonstrate any previous reports comparing the WOB_I of TT and ETT. In an attempt to clarify this phenomenon, we measured the WOB_I of ETT and TT in a lung model.

Materials and Methods

A patient model was assembled using an intubation mannequin* and a test lung (Fig. 1). The trachea of the mannequin was connected to one side of a two-chamber test lung via 10-mm-ID smooth-bore tubing. A lift bar was attached to the opposite chamber, which was ventilated by a Puritan-Bennett 7200ae ventilator. This allowed simulation of spontaneous breathing as first described by Op't Holt et al.[9] The 7200ae delivered a tidal volume (V_T) of 500 mL at a frequency (f) of 10 breaths/min with a descending flow waveform. Inspiratory flow was set at 0.5, 1.0, and 1.5 L/s to simulate quiet and labored breathing.

A computerized respiratory monitoring system (VenTrak) was used to measure flows and pressures for the calculation of WOB_I. A variable orifice pneumotachograph was placed at the proximal end of the ETT for measurement of flow. Pressure was measured by a Honeywell #143 PC03D pressure transducer. The pneumotachograph was characterized in the laboratory using a series of flows and volumes, creating a known response curve. This response curve was written into software and used by the monitor to allow accurate measurements of flow from 0.008 to 1.8 L/s. In order to measure WOB_I caused by the artificial airway, pressure was measured at the proximal airway and 4 centimeters distal to the tip of the artificial airway. The distal pressure-sensing site consisted of a 12-gauge flat-tip needle with side holes connected to the monitor by Tygon tubing. Calculations of WOB_I were accomplished by integrating V_T and distal pressure measurements, and WOB_I was defined as the area of the pressure-volume curve below baseline pressure. WOB_I is reported in J/L. Measurements were made with ETT and TT in the lung model (Table 1). These tubes were selected because they are carried on the intubation carts at University Hospital.

ETTs were placed in the intubation model in an attempt to create the characteristic 'question mark' shape assumed in vivo. ETT were placed 5 to 6 centimeters above the model's carina, the cuff was inflated, and the system was checked for leaks. TTs were placed through the top of the model trachea and positioned the same distance from the carina. The TT cuff was inflated and the model checked for leaks.

*Manufacturers or suppliers are identified in the Product Sources section at the end of the text.

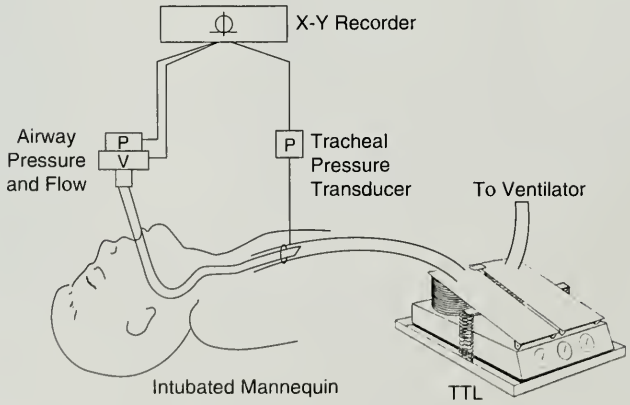


Fig. 1. Schema of the test system. Adapted from original figure by J Loos.

Table 1. Inside Diameter (ID), Length, and Dead Space of Artificial Airways Used in the Study

Tube	ID (mm)	Length (cm)	Dead Space (mL)
ETT #6*	6.0	31.5	11.0
ETT #7	7.0	34.5	15.0
ETT #8	8.0	35.5	18.0
ETT #8.5	8.5	36.5	24.0
TT Size 4†	5.0	10.0	3.0
TT Size 6	7.0	12.0	5.0
TT Size 8	8.5	12.0	6.0
TT Size 10	9.0	12.0	8.0

*ETT = endotracheal tube; TT = tracheostomy tube. Dead space = internal volume of tube.
† Note that tracheostomy tube size is not equal to inside diameter.

Measurements of WOB_I and peak negative pressure (PNP) were recorded for each ETT and TT at the three inspiratory flows (0.5, 1.0, and 1.5 L/s). PNP was obtained from proximal airway pressure measurements. All values are the mean of 10 measurements and are reported as mean (SD). Data were analyzed using analysis of variance for tubes of equivalent inside diameter (ID) and for the same tube at each flow setting.

Results

The WOB_I varied inversely with ID and directly with inspiratory flow (Fig. 2). At any laboratory condition, the WOB_I was lower with a TT than an ETT of equivalent ID. At flows of 1.0 and 1.5 L/s, this difference was statistically significant between 7.0- and 8.5-mm ETTs vs 7.0- and 8.5-mm TT ($p < 0.05$). Significant differences were seen in WOB_I and PNP ($p < 0.01$) for every 1-mm change in ETT ID at each flow. Likewise, each stepwise change in TT resulted in significant differences ($p < 0.01$) in WOB_I and PNP at each flow. For each tube (ET or TT), significant differences were seen in WOB_I and PNP for each increase in flow ($p < 0.01$). PNP also varied inversely with ID and directly with inspiratory flow (Fig. 3). Similarly, PNP was greater for ETT than TT of the same ID. This difference was significant for 7.0-mm ETT vs 7.0-mm TT at 1.0 L/s. The difference was also significant with 7.0- and 8.5-mm ETT compared to equivalent-sized TT at 1.5 L/s ($p < 0.05$).

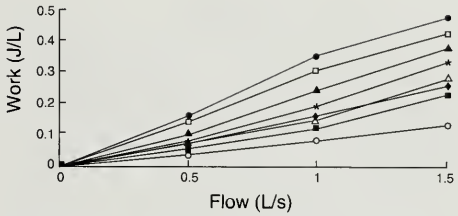


Fig. 2. The imposed work of breathing for each of the ETTs and TTs used in the study at inspiratory flows of 0.5, 1.0, and 1.5 L/s with a constant 0.4 L tidal volume. Tubes are designated by inside diameter (ID) in millimeters. ETT 6 = ●; TT 5 = □; ETT 7 = ▲; ETT 8 = ★; ETT 8.5 = △; TT 7 = ♦; TT 8.5 = ■; TT 9 = ○. Imposed work of breathing was significantly higher in ETT with ID of 7 and 8.5 mm than in TT of same ID at flows of 1.0 and 1.5 L/s. $p < 0.05$ for 7- and 8.5-mm ETT vs TT at 1 and 1.5 L/s.

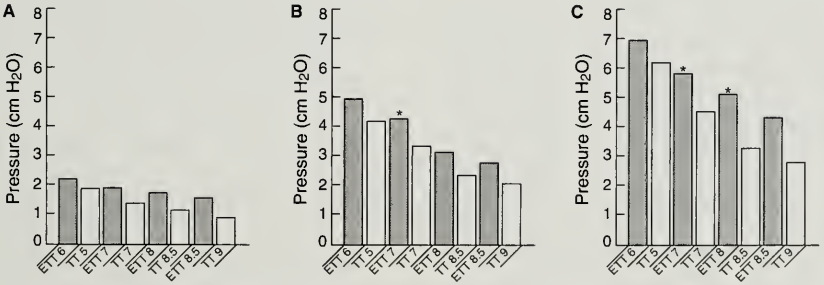


Fig. 3. Maximum negative pressure measured at the proximal airway with each ETT and TT used in the study at inspiratory flows of 0.5 L/s (A), 1.0 L/s (B), and 1.5 L/s (C). *$p < 0.05$ vs TT of equivalent ID. Tubes are designated by inside diameter in millimeters (not by size).

Discussion

Our results demonstrate a statistically significant decrease in WOB_I with use of a TT compared to an equivalent ID ETT as flow increased. The disparity in WOB_I became more pronounced as ID was reduced and inspiratory flow 'demand' increased.

The Hagen-Poiseuille equation states that under conditions of laminar flow, resistance varies inversely with the fourth power of the radius and is directly proportional to the length. Early studies of the ETT's effect on breathing concentrated on the increased resistance.[4,7,10] Using calculations of Reynolds number and Womersley number, Wright et al demonstrated that flow through ETTs is not laminar but turbulent.[3] This is in agreement with the work of Bolder et al.[1] However, Wright and colleagues found that the resistance of ETTs in vivo was significantly greater than in-vitro estimations would suggest. They attributed this finding to changes in the shape of thermolabile ETTs, the presence of secretions adherent to the lumen, and errors in in-vitro measurements due to the dissipation of kinetic energy.[3]

These results support our finding that WOB_I increases with decreasing ID and may account for changes between ETTs and TTs of equivalent ID. Our model allowed the ETT tube to be placed in the typical question mark shape seen in vivo. However, because the model remained at room temperature, our results may underestimate the true WOB_I. The increased length of ETTs also increases resistance and WOB_I compared to TTs. However, the contribution of increased length to resistance is small compared to changes in diameter.

Shapiro et al[2] measured the work of breathing (WOB) in normal subjects with an ETT placed "as far back in the pharynx as tolerable." They found WOB was inversely proportional to ID and directly proportional to increases in minute ventilation ($\dot{V}_E$). In subjects breathing through 6.0- and 7.0-mm-ID ETTs, they observed an increase in tension-time index approaching levels associated with diaphragmatic fatigue as $\dot{V}_E$ exceeded 20 L/min. They concluded that in patients with respiratory disease the effect of ETTs on WOB may be magnified.

Weissman et al[4] studied changes in ventilatory pattern associated with increased airway resistance in a group of normals and a group of patients following upper abdominal surgery. Patients and normal subjects breathed through resistors (5- to 15-mm ID) while V_T, $\dot{V}_E$, respiratory frequency (f), inspiratory flow, and inspiratory time were measured. Weissman et al[4] found that as ID diminished, f increased, V_T decreased, and $\dot{V}_E$ was preserved. They also found that with decreasing ID, there was a concomitant decrease in mean inspiratory flow and an increase in respiratory duty cycle (ie, inspiratory time).

Bolder et al[1] measured WOB_I with ETTs (5-, 6-, 7-, 8-, 9-, and 10-mm ID) in a lung model and found a 34-154% increase with a 1-mm decrease in ID. At similar V_T and inspiratory flow, Bolder et al's values for WOB_I are 20 to 30% less than ours. We believe that placing the ETT in the intubation mannequin results in increased resistance as the tube traverses the airway structures. This finding is in concert with the findings of Wright et al.[3]

In unison, these studies describe the potential danger of excessive WOB due to increased resistance from small ETTs.[1-4] The authors recommend use of the tube with the largest possible ID and warn of imminent problems during weaning from ventilatory support if the contribution of the ETT is unappreciated.[1-7]

Our clinical observation that patients occasionally wean quickly following tracheostomy resulted in performance of this study. We believe that the rigid, short length of the TT results in reduced resistance compared to the soft, thermolabile ETT, which is distorted as it travels through the upper airway. In our laboratory study, we found a significant decrease in WOB_I with TT, particularly at high inspiratory flow demands. These differences may be more pronounced in vivo than in our laboratory study due to patient temperature and the presence of secretions.

We have completed a pilot study measuring ventilatory variables in patients before and after tracheostomy.[11] This study demonstrated a small decrease in the mean (SD) WOB per breath, 1.04 (0.5) vs 0.85 (0.4) J/L, and a decrease in auto-PEEP, 3.2 (2) vs 2.0 (1.5) cm H_2O.[11] However, there were significant decreases in WOB/min, 12 (3) vs 7.3 (2.0) J/min, following tracheostomy ($p < 0.05$) and expiratory airway resistance (R_{awE}), 10.2 (7) vs 6.1 (3.4) cm $H_2O \cdot s^{-1} \cdot L^{-1}$ ($p < 0.01$).

The TTs and ETTs used in this study were chosen because they were available on all emergency airway kits in University Hospital. The differences in ID of the tubes deserve some explanation. Because a certain ratio of ID to outside diameter (OD) must be maintained to insure integrity of the tube, a size-6 TT has an ID of 7.00 mm, whereas a size-10 TT has an ID of 9.0 mm. In this study, only the 7-mm ETT and 6-mm TT, and 8.5-mm ETT and 8-mm TT have equivalent diameters. However, by drawing a line between datapoints from lowest ID to highest ID for both TT and ETT, it is obvious that the TT has a lower WOB_I. Clinicians should be aware that while the number of an ETT is equivalent to its ID, the same is not true for TT.

Our results support the work of others (ie, the artificial airway can contribute to ventilatory inefficiency due to increased airway resistance and WOB). Eliminating ETT resistance can be accomplished by noninvasive face mask ventilation[12,13] or overcome by using pressure support[14-16] or triggering the ventilator at the distal tip of the ETT.[17,18] Our findings also suggest that tracheostomy may provide a more suitable airway and aid in weaning of selected patients. We do not recommend early tracheotomy as a technique to decrease the WOB but rather suggest that in patients with repeated weaning failures tracheotomy may be considered as an adjunct to liberation from the ventilator.

More recently, Guttmann et al[19] have developed a computer-assisted method that allows ETT resistance to be determined from the known pressure-flow relationships of the tubes, proximal airway pressure and inspiratory flow. This allows the ventilator to provide the required level of pressure to negate WOB_I. All of these methods require continued mechanical ventilatory support. This study was undertaken to compare the differences in WOB_I during spontaneous breathing.

PRODUCT SOURCES

Endotracheal Tubes:
Sheridan Catheter, Argyle NY

Tracheostomy Tubes:
Shiley low pressure cuffed tracheostomy tubes, Shiley Inc, Irvine CA

Intubation Mannequin:
Adult Intubation Model, Laerdal Medical Corp, Tuckahoe NY

Monitor:
VenTrak Respiratory Monitor, Novametrix, Wallingford CT

Pressure Transducer:
#143 PC03D, Honeywell, Dayton OH

Statistical Software:
SPSS/PC+, SPSS Inc, Chicago IL

Test Lung:
TTL, Michigan Instruments, Grand Rapids MI

Ventilator:
Puritan-Bennett 7200ae, Puritan-Bennett Corp, Carlsbad CA

REFERENCES

1. Bolder PM, Healy TEJ, Bolder AR, Beatty PC, Kay B. The extra work of breathing through adult endotracheal tubes. Anesth Analg 1986;65(8):853-859.
2. Shapiro M, Wilson RK, Casar G, Bloom K, Teague RB. Work of breathing through different sized endotracheal tubes. Crit Care Med 1986;14(12):1028-1031.
3. Wright PE, Marini JJ, Bernard GR. In vitro versus in vivo comparison of endotracheal tube airflow resistance. Am Rev Respir Dis 1989;140(1):10-16.
4. Weissman C, Askanazi J, Rosenbaum SH, Damask MC, Hyman AI, Kinney JM. Response to tubular airway resistance in normal subjects and postoperative patients. Anesthesiology 1986;64(3):353-358.
5. Ooi R, Fawcett WJ, Soni N, Riley B. Extra inspiratory work of breathing imposed by cricothyrotomy devices. Br J Anaesth 1993;70(1):17-21.
6. Chiaranda M, Rossi A, Manani G, Pinamonti O, Braschi A. Measurement of the flow-resistive properties of double-lumen bronchial tubes in vitro. Anaesthesia 1989; 44(4):335-340.
7. Gal TJ, Suratt PM. Resistance to breathing in healthy subjects following endotracheal intubation under topical anesthesia. Anesth Analg 1980;59(4):270-274.
8. Pride NB. The assessment of airflow obstruction: role of measurements of airways resistance and of tests of forced expiration. Br J Dis Chest 1971;65:135-169.
9. Op't Holt TB, Hall MW, Bass JB, Allison RC. Comparison of changes in airway pressure during continuous positive airway pressure (CPAP) between demand valve and continuous flow devices. Respir Care 1982;27 (10):1200-1209.
10. Southgate MT. Airflow resistances of endotracheal tubes (editorial). JAMA 1977;237(13):1362.
11. Davis K, Campbell RS, Branson RD, Johnson DJ, Valente JF, Porembka D. Changes in respiratory mechanics following tracheostomy (abstract). Crit Care Med 1993; 21:S211.
12. Brochard L, Isabery D, Piquet J, Amaro P, Mancebo J, Messadi AA, et al. Reversal of acute exacerbations of

chronic obstructive lung disease by inspiratory assistance with a face mask. N Engl J Med 1990;323(22): 1523-1530.
13. Meduri GU, Conoscenti CC, Menashe P, Nair S. Noninvasive face mask ventilation in patients with acute respiratory failure. Chest 1989;95(4):865-870.
14. Fiastro JF, Habib MP, Quan SF. Pressure support compensation for inspiratory work due to endotracheal tubes and demand continuous positive airway pressure. Chest 1988;93(3):499-505.
15. Bersten AD, Rutten AJ, Vedig AE, Skowronski GA. Additional work of breathing imposed by endotracheal tubes, breathing circuits, and intensive care ventilators. Crit Care Med 1989;17(7):671-677.
16. Brochard L, Rua F, Lorino H, Lemaire F, Harf A. Inspiratory pressure support compensates for the additional work of breathing caused by the endotracheal tube. Anesthesiology 1991;75(5):739-745.
17. Banner MJ, Kirby RR, Blanch PB. Site of pressure measurement during spontaneous breathing with continuous positive airway pressure: effect on calculating imposed work of breathing. Crit Care Med 1992;20(4):528-533.
18. Banner MJ, Blanch PB, Kirby RR. Imposed work of breathing and methods of triggering a demand-flow, continuous positive airway pressure system. Crit Care Med 1993;21:183-190.
19. Guttmann J, Eberhard L, Fabry B, Bertschmann W, Wolff G. Continuous calculation of intratracheal pressure in tracheally intubated patients. Anesthesiology 1993;79(3):503-513.

American Association for Respiratory Care
40th Annual Convention and Exhibition
December 10-13, 1994 • Las Vegas, Nevada

Evaluation of a Prototype Expiratory-Phase Aerosol Controller during Simulated Pediatric Volume-Controlled Ventilation

Jim Keenan BS RRT and John W Salyer BS RRT

BACKGROUND: Some methods of administering aerosolized medications during volume-controlled ventilation require adjusment of ventilator settings to avoid inadvertent increases in tidal volume (V_T). Our bench evaluation of an expiratory-phase aerosol controller (EXPAC) sought to determine the differences (1) in aerosol delivery between continuous and EXPAC nebulization in pediatric and neonatal ventilator circuits and (2) in delivered V_T with a 30-cm vs a 213-cm nebulizer supply line. DESCRIPTION OF DEVICE: An electrically powered EXPAC linked to the VIP Bird ventilator by a fiberoptic cable and driven by flow from an integral blender was developed to our performance specifications. EVALUATION METHODS: In Phase 1, V_T was measured at the patient connection under 3 conditions: (1) no nebulizer in-line, (2) a dry in-line nebulizer driven by EXPAC with a 30-cm supply line, and (3) Condition 2 with a 213-cm supply line. In Phase 2, we measured the aerosol delivered to a filter placed between the patient connector and the test lung. Aerosol delivery = filter wet weight – filter dry weight. RESULTS: (1) When EXPAC was operated according to manufacturer's recommendations, no significant differences were found between V_Ts measured with EXPAC plus the 30-cm line and with no nebulizer in-line. V_T increased significantly ($p = 0.0001$, 1-way ANOVA) in both circuits with the 213-cm supply line. (2) Mean (SD) aerosol delivery at the patient connection of the pediatric circuit was 1.5 (0.002) % with EXPAC and 1.7 (0.003) % with continuous nebulization ($p = 0.23$, t test) and of the neonatal circuit 1.6 (0.002) % with EXPAC and 1.5 (0.002) % with continuous nebulization ($p = 0.45$, t test). CONCLUSIONS: EXPAC eliminated need for adjustment of ventilator settings and according to our data was as effective as continuous nebulization for delivering aerosol to the patient connection. [Respir Care 1994;39(6):617-622.]

Background

The administration of nebulized medications to infants and children during mechanical ventilation has become a widespread practice.[1] Many techniques have been described, but it is reported that more than 50% of neonatal and pediatric applications involve placing a nebulizer into the mechanical ventilator circuit.[1] This technique has been shown to be at least as effective as, if not better than, the use of manual ventilation during the procedure.[2,3] When a continuous-flow aerosol is administered in-line with the ventilator circuit (ie, flow through the circuit during inspiration and exhalation), ventilator function is affected.[4] With a volume ventilator, adjustments to tidal volume (V_T) must be made to prevent inadvertent increases because, in some cases, nebulizer flow increases V_T. These inadvertent increases in V_T can be clinically important.[5,6]

Mr Keenan is Clinical Educator and Mr Salyer is Director, Respiratory Care Service, Primary Children's Medical Center, Salt Lake City, Utah.

The authors have no financial interest in any of the products mentioned in the text.

Reprints: Jim Keenan RRT, Respiratory Care Service, Primary Children's Medical Center, 100 North Medical Dr, Salt Lake City UT 84113.

One way that clinicians have dealt with this difficulty is to manually adjust the ventilator so that V_T remains constant during the treatment. Unfortunately, if the clinician fails to make this adjustment either before or after the aerosol is given, inadvertent increases (during the treatment) or decreases (after the treatment) in V_T will occur. Reducing V_T may cause elevation of P_{aCO_2}. Increasing V_T places the patient at risk for volutrauma. In our experience, many clinicians, from recent graduates to experienced practitioners, have made these errors.

Another possible solution for this problem is a system designed so that nebulization occurs only during the expiratory phase of the ventilator cycle.[7] When inspiration begins, the volume of gas in the inspiratory limb of the ventilator circuit, acting as an inspiratory aerosol reservoir, is charged with aerosol particles. No additional flow is added to the circuit because nebulization stops when inspiration begins. It has previously been shown that placement of the nebulizer in the inspiratory limb some distance from the patient connection improves aerosol delivery in both adult and pediatric circuit configurations.[8,9]

The development of expiratory-phase nebulization technology for the Servo 900C ventilator was reported in a study conducted by Dahlbach et al.[7] However, this application requires extensive electromechanical modifications of the ventilator and further, in our experience, the 900C is not well suited for volume ventilation of spontaneously breathing pediatric patients who weigh < 15 kg, presumably because of the demand valve's relatively slow response time.[10,11]

Description of Device

A prototype expiratory-phase aerosol controller (EXPAC) was developed based on our request and recommended performance specifications using a commercially available inspiratory-phase aerosol controller.* This EXPAC is electrically powered and pneumatically driven by gas flow from the ventilator's integral blender. Flow range is 2-9 L/min and can be adjusted to regulate aerosol output and to accommodate a variety of manufactured updraft aerosol nebulizers. EXPAC is used to administer aerosol to mechanically ventilated patients and operates only during the expiratory phase of a mechanical breath. EXPAC functions with the VIP Bird ventilator using a fiberoptic transmission cable. We report the results of a study of aerosol delivery using a prototype EXPAC in a bench model of pediatric mechanical ventilation.

*Manufacturers and suppliers are identified in the Product Sources section at the end of the text.

Evaluation Methods

Two circuit configurations were used—neonatal and pediatric. These configurations correspond to our clinical practice, in which we use the neonatal circuit for patients who require $V_T < 100$ mL and the pediatric circuit for those who need $V_T > 100$ mL. The disposable neonatal circuit is 120 cm long and is made of 1-cm-diameter corrugated plastic tubing with a compressible volume of 0.83 mL/cm H_2O. The disposable pediatric circuit is 120 cm long and is made of 1.5-cm-diameter corrugated plastic tubing with a compressible volume of 1.20 mL/cm H_2O. Both circuits contained heating wires in both their inspiratory and expiratory limbs, but the circuits were not heated during the experiments. The same nebulizer was used during all experiments to avoid the influence of variability that may have existed among nebulizers on our measurements.[12,13] We used 6 L/min flow from the ventilator's internal flowmeter and therefore were able to maintain the same F_{IO_2}. In all experiments, a humidifier was placed in the circuit but was not filled with water or powered, so that water vapor from the humidifier would not add to the saturation of the filter and give a falsely high aerosol delivery value when the filter was weighed. In our hospital, when in-line aerosols are administered, the humidifier is placed in standby mode as recommended by the manufacturer. The standby mode disables the servo mechanism and maintains the temperature in the humidifier between 32° and 36° C.

Phase 1

The manufacturer of EXPAC recommends that the gas-supply tubing be less than 30-cm long. They believe that V_T may increase markedly with a longer supply line because it has the capacity to

Table 1. Volume-Controlled Ventilator Test Conditions for Neonatal and Pediatric Circuit Configurations during Phase 1: Tidal Volume (V_T) Measurements

Ventilator Variables	Neonatal Circuit	Pediatric Circuit
Rate (breaths/min)	20	8
Set V_T (mL)	80	210
Compressible volume (mL/cm H_2O)	0.83	1.20
Flow (L/min)	10	16
t_I (s)	0.5	0.8
PEEP (cm H_2O)	4	4

hold a measurable volume of gas under pressure during the expiratory phase. Therefore, we decided to test the company's recommendation and speculation by comparing V_T using a 30-cm and a 213-cm length of supply tubing on both the neonatal and pediatric configurations. Table 1 lists the ventilator settings used for each circuit configuration during Phase 1 of our study. We sought to determine whether V_T remained constant (with no manipulation of the ventilator settings) when a nebulizer was placed in the inspiratory limb of the ventilator circuit and driven by EXPAC with a 30-cm supply line and then with a 213-cm supply line. The latter is that normally supplied with the nebulizer. All other conditions were held constant throughout Phase 1 of the study.

Delivered V_T was measured 6 times at each experimental condition, using a resistive-orifice pneumotachometer linear over 0-35 L/min flow.[14] The pneumotachometer was calibrated volumetrically before each run using a 2-point calibration. During this phase, the nebulizer was operated dry to avoid condensation of the aerosol on the pneumotachometer screens. The experimental setup is shown in Figure 1.

Phase 2

During Phase 2, the delivery of aerosolized solution to the filter at the patient connection was compared using both types of nebulization in both a pediatric and neonatal circuit configuration. Experimental set up was as in Phase 1 (Fig. 1). A filter, capable of trapping particles $\geq 0.02\ \mu$ in size,[15] was weighed and then placed between the patient connection and the test lung. The nebulizer was weighed empty and then again after the addition of 3.0 mL of normal saline and 0.5 mL of albuterol sulfate. It was placed in the inspiratory limb of the circuit at the outflow connection of the humidifier and was run either continuously (conventional method) or during the expiratory phase only (using EXPAC) until the cup was dry (ie, there was no audible or visual evidence of continued nebuliza-

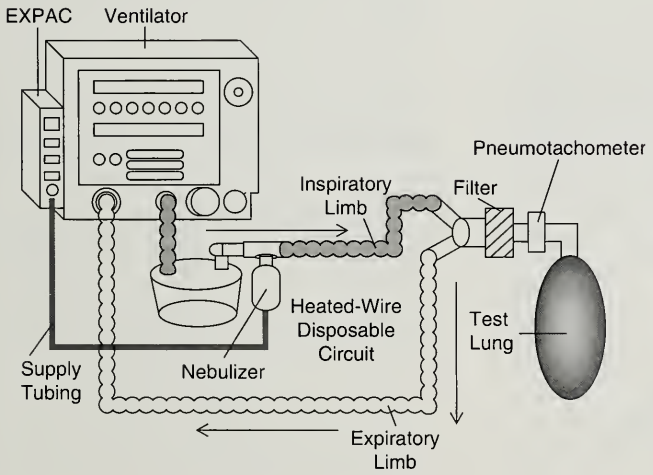


Fig. 1. Schema of the ventilator-test lung configuration used to measure aerosol delivery and tidal volume.

tion) for a period of at least 30 seconds. The nebulizer was periodically tapped and shaken, as we do clinically, to cause droplets that adhere to the side to fall to the bottom of the cup.[16] Flow was stopped when nebulization was complete and the filter was removed and weighed. Percent delivered was calculated.

$$(\text{delivered}/\text{deliverable}) \times 100\% = \%\ \text{delivered},$$

where deliverable aerosol = [nebulizer dry – nebulizer with dose] and delivered aerosol = [filter weight pre – filter weight post nebulization].

This procedure was repeated 5 times for each test condition (continuous nebulization vs EXPAC) using two circuit configurations (pediatric and neonatal). The specific ventilator settings for both test conditions are given in Table 2.

Table 2. Volume-Controlled Ventilator Test Conditions for Neonatal and Pediatric Circuit Configurations during Phase 2: Aerosol Delivery

Ventilator Variable	Neonatal Circuit	Pediatric Circuit
Rate (breaths/min)	18	12
Set V_T (mL)	80	300
Compressible volume (mL/cm H_2O)	0.83	1.20
Flow (L/min)	10	23
I_I (s)	0.5	0.8
PEEP (cm H_2O)	4	4

Statistical Analysis

In Phase 1, V_T was measured without nebulization and during expiratory-phase nebulization, with both short and long nebulizer gas-supply lines. Mean values of 6 measurements under each condition were compared using a one-way analysis of variance for each circuit configuration.[17]

During Phase 2, aerosol delivery was estimated by weighing the filters before and after nebulization. The means of 5 measurements taken with each aerosol delivery mode were compared to each other using an independent *t* test for each circuit configuration. Null hypotheses were rejected when the probability of rejecting a true null was < 0.05.

Evaluation Results

Tables 3 and 4 contain our results. In Phase 1, we found that when the 30-cm supply line was used with EXPAC, there were no clinically important or statistically significant differences in V_T between that delivered without the nebulizer in-line and that when EXPAC was operating. However, EXPAC with a 213-cm supply line resulted in a statistically significant increase in V_T from that delivered without the in-line nebulizer of 33 and 40% for the pediatric and neonatal circuits, respectively ($p = 0.0001$, both configurations). These values for both circuit configurations are given in Table 3.

In Phase 2, we found no statistically significant or clinically important difference in the absolute weight of aerosol delivered to the patient connection whether the nebulizer was operated continuously or only during the expiratory phase ($p > 0.05$, both configurations). These data are presented in Table 4.

Discussion

Our study shows that the use of expiratory-phase nebulization has no effect on V_T when compared to

Table 3. Results of Phase 1: Measured Tidal Volume (V_T) under Three Conditions—Data Are Mean (SD) in mL

	Condition 1*	Condition 2†	Condition 3‡	p Value§
Neonatal circuit	63.0 (0.63)	66.5 (2.07)	93.3 (0.816)	0.0001
Pediatric circuit	181.0 (0.63)	187.0 (1.10)	214.8 (0.41)	0.0001

*Condition 1— no nebulizer in-line.
†Condition 2—nebulizer in-line with 30-cm supply line.
‡Condition 3—nebulizer in-line with 213-cm supply line.
§1-way analysis of variance.

Table 4. Results of Phase 2: Change in Filter Weight (g) as a Result of Continuous vs Expiratory Nebulization—Data Are Mean (SD)

Circuit	Continuous Nebulization	Expiratory Nebulization	p Value*
Neonatal	0.051 (0.008)	0.056 (0.007)	0.45
Pediatric	0.058 (0.009)	0.052 (0.006)	0.26

*Independent *t* test (2-side).

V_T delivered when no nebulizer is in-line. An EXPAC is more convenient compared to the more common method of continuous-flow nebulization because no ventilator adjustments are necessary. The possibility of failing to adjust the ventilator settings (risking volutrauma or hypoventilation) before or after the aerosol treatment is eliminated. The presence of an integral blender enables delivery of a consistent F_{IO_2}. Based on these findings, we speculate that EXPAC improves patient safety during in-line aerosol administration.

Indeed, Dahlback and colleagues[7] report the use of an expiratory-phase nebulizer controller with a modified Servo 900C. Some pediatric ventilator manufacturers have addressed this problem in another fashion. The Newport Wave has the ability to provide inspiratory-phase aerosol nebulization in the volume mode. No ventilator adjustments are required because some of the ventilator's set flow is rerouted to drive the nebulizer during inspiration so the total flow is not changed. The Newport Breeze is supplied with an auxiliary flowmeter to provide the same F_{IO_2} but, as with any additions of flow into the circuit, ventilator adjustments must be made to prevent inadvertent increases in V_T.

The design of EXPAC is such that the use of a gas-supply tube longer than 30 cm may cause a clinically important increase in V_T. We included a 213-cm supply line in our study because this was the standard tubing length that is supplied with the brand of disposable hand-held nebulizer we use. In view of these data, we do not recommend the use of a supply line longer than 30 cm.

Rau and Harwood[2] reported that only 1.68% of nebulized medication was delivered to the end of the endotracheal tube, as compared to our findings of 1.5-1.7 % delivery. MacIntyre reported a deposition of 2.9% in an adult in-vitro study.[18] However, these comparisons must be interpreted cautiously because of important methodologic differences among our studies. For example, we measured delivery at the patient connection, whereas Rau and Harwood[2] measured it at the distal end of the endotracheal tube. Becaue of this, one would expect that the proportion of aerosol delivered in our study would be considerably higher than theirs. However, the placement of our nebulizer at the humidifier outlet, which was necessary to charge the inspiratory circuit with aerosol, dictated that the aerosol traverse the entire length of the inspiratory circuit and may have contributed to loss of aerosol by condensation.

We believe that in-line nebulization is generally superior to manual ventilation for aerosol administration. Deposition notwithstanding, manual ventilation may be poorly tolerated by patients. Some evidence suggests that deposition with in-line aerosol administration is at least equivalent to that with manual ventilation.[6]

Although not an a priori hypothesis, we observed that administration time was longer when EXPAC was used and appeared to vary directly with mechanical breathing rate (and therefore inversely with expiratory time). However, at a set rate of 20 breaths/min, administration time was less than 15 minutes.

One limitation of our model was that it did not mimic a spontaneously breathing patient; thus, we are unable to speculate on the performance of EXPAC in such patients. However, we do speculate that the percentage of aerosolized medications deposited at the patient connection would vary directly with spontaneous respiratory rate.

We did not test EXPAC in an adult model and it may be suitable only for pediatric patients. With adult patients, the aerosol-laden bolus of gas in the inspiratory limb of the circuit would surely be less than V_T and the volume of gas in the inspiratory limb must be $\geq V_T$ for both mechanical and spontaneous breaths to be fully saturated with aerosol.[7]

A comprehensive discussion of the factors that influence aerosol delivery and deposition during the administration of aerosols with mechanical ventilators is beyond the scope of this paper. We refer the reader to Hess' recent review of this topic.[19]

Conclusions

The use of this prototype EXPAC in conjunction with pediatric applications of volume-controlled ventilation could accomplish some important objectives: (1) It could permit the insertion of an in-line nebulizer without requiring an adjustment in set V_T or F_{IO_2} as long as the 30-cm supply tubing is used and (2) it would deliver aerosol to the patient connection at least as efficiently as continuous nebulization in our model. The presence of humidity may affect aerosol delivery differently with the two systems. However, broad conclusions about the performance of these aerosol controllers cannot be derived from our experience, but instead require testing of a number of production models of this device.

PRODUCT SOURCES

Ventilators:
VIP Bird, Bird Products Corp, Palm Springs CA
Servo 900C, Siemens-Elema, Schaumburg IL
Newport Wave and Newport Breeze, Newport Medical Instruments Inc, Newport Beach CA

Aerosol Controller:
Bird Products Corp, Palm Springs CA

Humidifier:
Fisher & Paykel, Model 700, Auckland, New Zealand

Nebulizer:
Marquest Whisper Jet Nebulizer, Marquest Medical Products, Englewood CO

Ventilator Circuits:
Isothermal Industries, Riverside CA

Air/Oxygen Blender:
Bird Products Corp, Palm Springs CA

Filter:
BB-50T, Pall Biomedical Inc, East Hills NY

Volume Measuring Device:
StarCalc, Infrasonics Inc, San Diego CA

Statistical Software:
Statview v.2.0, Abacus Concepts, Berkeley CA

REFERENCES

1. Salyer JW, Chatburn RL. Patterns of practice in neonatal and pediatric respiratory care. Respir Care 1990;35(9): 879-888.
2. Rau JL Jr, Harwood RJ. Comparison of nebulizer delivery methods through a neonatal endotracheal tube: a bench study. Respir Care 1992;37(11):1233-1240.
3. Flavin M, MacDonald M, Dolovich M, Coates G, O'Brodovich H. Aerosol delivery to the rabbit lung with an infant ventilator. Pediatr Pulmonol 1986;2(1):35-39.
4. Hanhan U, Kissoon N, Payne M, Taylor C, Murphy S, DeNicola LK. Effects of in-line nebulization on preset ventilatory variables. Respir Care 1993;38(5):474-478.
5. Salyer JW, Rosolowski B, O'Loughlin L, Chatburn RL. The effect of continuous in-line nebulization on tidal volume during volume ventilation of an infant lung model (abstract). Respir Care 1990;35(11):1121.
6. Henry WD, Chatburn RL. Effects of manual versus mechanical ventilation on aerosol dose efficiency (abstract). Respir Care 1988;33(10):914.
7. Dahlback M, Wollmer P, Drefeldt B, Jonson B. Controlled aerosol delivery during mechanical ventilation. J Aerosol Med 1989;2:339-347.
8. Hughes JM, Saez J. Effects of nebulizer mode and position in a mechanical ventilator circuit on dose efficiency. Respir Care 1987;32(12):1131-1135.
9. Brown WR, Nystrom GA, Hopper AO, Deming DD. Aerosol generator performance in an infant ventilator circuit (abstract). Respir Care 1989;34(11):1025,1027.
10. Salyer JW, Lynch JM, Timmons O, Watkins C, Keenan J. Response time in two brands of pediatric ventilators (abstract). Respir Care 1992;37(11):1331-1332.
11. Martin LD, Rafferty JF, Wetzel RC, Gioia FR. Inspiratory work and response times of a modified pediatric volume ventilator during synchronized intermittent mandatory ventilation and pressure support ventilation. Anesthesiology 1989;71(6):977-981.
12. Marquest nebulizer performance specifications Inspire No. 45. Englewood CO: Marquest Medical Products 1989.
13. Clay MM, Pavia D, Newman SP, Clarke SW. Factors influencing the size distribution of aerosols from jet nebulizers. Thorax 1983;38(10):755-759.
14. StarCalc Operator's Manual. San Diego CA: Infrasonics Inc, 1989.
15. Ball PR, Berman LS, Saunders D. Viral removal by Pall breathing circuit filters. Glen Cove NY: Pall Biomedical Products Corp, 1988.
16. Hess D, Horney D, Snyder T. Medication-delivery performance of eight small-volume, hand-held nebulizers: effects of diluent volume, gas flowrate, and nebulizer model. Respir Care 1989;34(8):717-723.
17. Dawson-Saunders B, Trapp RG. Basic and clinical biostatistics, 1st ed. Norwalk CT: Appleton & Lange, 1990.
18. MacIntyre NR, Silver RM, Miller CW, Schuler F, Coleman RE. Aerosol delivery in intubated, mechanically ventilated patients. Crit Care Med 1985;13(2):81-84.
19. Hess D. Inhaled bronchodilators during mechanical ventilation: delivery techniques, evaluation of response, and cost-effectiveness. Respir Care 1994;39(2):105-122.

Expiratory Hold vs Clamping/Transducing for Intrinsic PEEP Determination in the Siemens 900C

Deborah Madsen RRT, Kelly Jager RRT, John Fenwick MD, and Martin Tweeddale MB

BACKGROUND: Various investigators have commented on the possible underestimation of intrinsic PEEP ($PEEP_i$) when the expiratory hold function on microprocessor ventilators equipped with high-compressible-volume circuits is used. Although several ventilators incorporate this method of measuring $PEEP_i$, comparisons with other accepted methods have been infrequent. METHODS: In an in-vitro lung model, we examined the difference between the clamping/transducing method and the use of the expiratory hold function of the Siemens 900C ventilator equipped with a low-compressible-volume circuit. Seven different $PEEP_i$ levels ranging from 3-26 cm H_2O were generated through random alterations in minute ventilation and inspiratory to expiratory ratio. For each method the measurement was repeated three times at each level of $PEEP_i$. Data analysis was performed employing the technique of Bland. RESULTS: The mean (SD) difference between the two methods was –0.13 (1.14) cm H_2O, a value close to zero showing good agreement between the two methods. The mean difference between the two methods did not increase as $PEEP_i$ increased. The maximum difference between the two methods of determining $PEEP_i$ lay within ±2 standard deviations of the mean, that is, within ±2.28 cm H_2O. This value is within a predetermined clinically acceptable range of ±2.5 cm H_2O. CONCLUSION: In this laboratory study, we found no significant difference in the results obtained with $PEEP_i$ measurement using the clamping/transducing method and with the expiratory hold function of the Siemens 900C ventilator when the ventilator is equipped with a low-compressible-volume circuit. [Respir Care 1994;39(6):623-626.]

Introduction

Intrinsic PEEP ($PEEP_i$) is an unintentional positive end-expiratory pressure at the alveolar level that develops in patients receiving mechanical ventilation when time for exhalation is inadequate.[1] Potential adverse effects of $PEEP_i$ include barotrauma, hemodynamic compromise, misinterpretation of central venous pressures, increased work of breathing, and miscalculation of respiratory system compliance.[1,2] The detection and accurate measurement of $PEEP_i$ are therefore crucial for the optimal management of patients receiving mechanical ventilation.

Techniques employed for the detection and measurement of $PEEP_i$ include the clamping/transducing method and the use of the expiratory hold function on third-generation ventilators.[2] Grootendorst et al[3] found a significant underestimation of $PEEP_i$ as measured by the expiratory hold function of the Siemens 300 ventilator when compared with the clamping/transducing method. This underestimation of $PEEP_i$ was attributed to the high-compressible-volume circuit of the Siemens 300 ventilator

Ms Madsen is a Charge Therapist and Ms Jager is Clinical Staff Development Coordinator in the Respiratory Services Department, Dr Fenwick is Associate Director, Intensive Care Unit, and Dr Tweeddale is Director, Intensive Care Unit—Vancouver General Hospital, Vancouver, British Columbia, Canada.

The authors have no financial interest in the products mentioned in the study.

A version of this paper was presented by Ms Madsen during the RESPIRATORY CARE OPEN FORUM at the 1993 AARC Annual Meeting, held in Nashville, Tennessee.

Reprints: Deborah Madsen RRT, Respiratory Services Department, Vancouver General Hospital, Heather Pavilion Tunnel, 855 West 12th Ave, Vancouver, British Columbia, Canada V5Z 1M9.

used in their study. Our clinical impression has been that this underestimation of $PEEP_i$ is not seen when low-compressible-volume circuits are employed with the Siemens 900C ventilator. To confirm our clinical impression we therefore examined, in an in-vitro lung model, the difference between the measurement of $PEEP_i$ obtained by the clamping/transducing method and by the expiratory hold function of the Siemens 900C ventilator equipped with a low-compressible-volume circuit.

Methods

Materials

A Siemens 900C ventilator with a low-compressible-volume circuit having a measured compliance of 1.8 mL/cm H_2O was connected to a test lung (Vent Aid, Michigan Instruments, Grand Rapids MI) via an 8.5-mm endotracheal tube. The humidifier was turned off for the study. A #7.7 parabolic resistor (Pneuflo, Michigan Instruments) was placed on each bronchus of the test lung to mimic a patient with increased airways resistance. The compliance of the test lung was set at either 50 or 80 mL/cm H_2O, and seven different $PEEP_i$ levels ranging from 3 to 26 cm H_2O were generated by random alterations in minute ventilation and inspiratory-to-expiratory ratio.

Protocol

$PEEP_i$ was measured using both the clamping/transducing method and the expiratory hold function of the ventilator. For the measurement of $PEEP_i$ by the clamping/transducing method, airway pressures were transduced at the flex tube via an 18-cm length of pressure tubing connected to a disposable pressure transducer (TXXX-R, Canadian Cardiovascular, Ontario, Canada) and displayed on a cardiac monitor/recorder (Fig. 1). The transducer was referenced to atmospheric pressure and zeroed prior to each set of measurements. The flex tube was manually clamped at end-exhalation, and $PEEP_i$ was obtained from paper recordings of end-expiratory airway pressure. Acceptable $PEEP_i$ measurements required clamping of the flex tube within 0.2 seconds of end-exhalation and the recording of a clearly defined airway pressure plateau (Fig. 2). The measurement was repeated three times at each level of $PEEP_i$ with a 2-minute interval between each measurement.

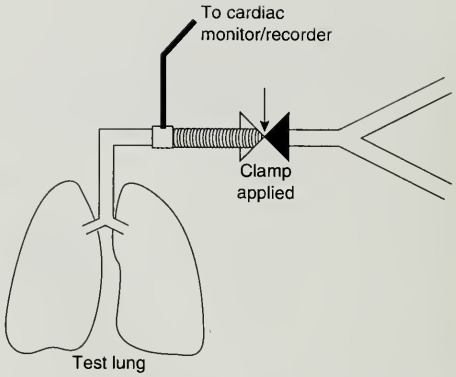


Fig. 1. For the measurement of $PEEP_i$ by the clamping/transducing method, the flex tube was manually clamped at end-exhalation and $PEEP_i$ was obtained from paper recordings of end-expiratory airway pressure.

For the measurement of $PEEP_i$ using the expiratory hold function of the ventilator, the manometer was first calibrated as outlined in the Siemens 900C operating manual.[4] At each level of $PEEP_i$ generated, the expiratory hold button was depressed for 4 seconds and the $PEEP_i$ was read from the ventilator manometer and recorded. The measurement was repeated three times at each level of $PEEP_i$ with a 2-minute interval between each measurement.

Data Analysis

For each measurement of $PEEP_i$, the difference between the values obtained by each method was calculated and plotted against the mean of the same two values, as described by Bland.[5] Two conditions must be met for the two methods of $PEEP_i$ measurement to be considered equivalent. First, the mean difference for all estimates of $PEEP_i$ must be close to zero, and second, the standard deviation of the mean difference must be small enough that all data points be within a clinically acceptable range. A difference between the two methods of $PEEP_i$ measurement of ±2.5 cm H_2O was considered clinically acceptable.

Results

The mean (SD) difference between the two methods of $PEEP_i$ measurement was –0.13 (1.14) cm

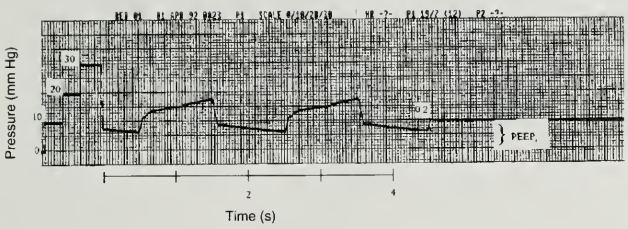


Fig. 2. Paper recording of airway pressure versus time for a single trial of PEEP$_i$ measurement by the clamping/transducing method. An acceptable PEEP$_i$ measurement required clamping of the flex tube within 0.2 seconds of end-exhalation and the recording of a clearly defined airway pressure plateau.

H_2O with a 95% confidence interval of −0.64 to 0.39 (Table 1). This value was close to zero, indicating good agreement between the two methods. The mean difference between the two methods of measurement did not increase as the PEEP$_i$ increased. The maximum difference between the two methods of determining PEEP$_i$ lay within ±2 standard deviations of the mean, that is, within ±2.28 cm H_2O (Fig. 3). This value is within our predetermined clinically acceptable range of ±2.5 cm H_2O.

Discussion

The major finding of this study is that there is no difference between the measurement of PEEP$_i$ using the clamping/transducing method and the expiratory hold function of the Siemens 900C ventilator when the ventilator is equipped with a low-compressible-volume circuit (1.8 mL/cm H_2O).

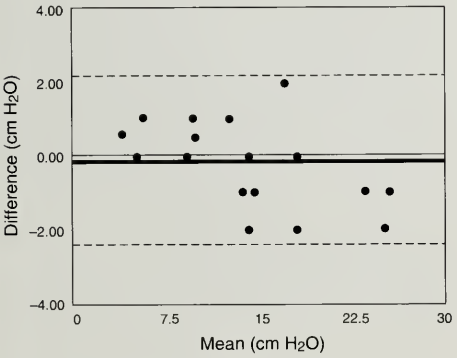


Fig. 3. The difference between the values obtained by each method of PEEP$_i$ measurement plotted against the mean of the same two values. The mean difference between the two methods is identified by the thick solid line. The dotted lines identify the 2 standard deviation values above and below the mean.

We are unaware of any other laboratory study comparing these two methods of PEEP$_i$ measurement. In a clinical study of 5 patients with lung compliances ranging from 8 to 20 mL/cm H_2O, Grootendorst et al[3] found a significant underestimation of PEEP$_i$ as measured by the expiratory hold function of the Siemens 300 ventilator when compared with the clamping/transducing method. This underestimation of PEEP$_i$ was attributed to the high-compressible-volume circuit (6 to 8 mL/cm H_2O) used in their study. Our finding no difference between the two methods of PEEP$_i$ measurement with the use of a low-compressible-volume-circuit supports this conclusion. However, our use of a Siemens 900C ventilator and the higher compliance range of our test lung could also account for the difference between our results and theirs. Because the Siemens 300 and 900C ventilators have identical expiratory hold mechanisms, this cannot account for the different findings.[4] Although our test-lung compliance was significantly higher than the lung compliances of the patients studied by Grootendorst et al, we generated PEEP$_i$ levels as high as 26 cm H_2O and found no increase in the mean difference between the two methods of measurement even at these high PEEP$_i$ levels. In addition, preliminary clinical work suggests that this laboratory finding also applies in patients with lung compliances in the range studied by these investigators.

Use of the expiratory hold function of the Siemens 900C ventilator has several advantages over the clamping/transducing method for the measurement of PEEP$_i$. First, far less time is required for obtaining a measurement, usually less than 5 seconds. Second, human error is avoided as the inspiratory/expiratory scissors automatically close at

Table 1. Values of Intrinsic PEEP by Two Methods, Means of and Differences between Those Values

Trial Number	Method		Mean	Difference
	Clamping/Transducing	Expiratory Hold		
1a	15	14	14.5	−1
1b	14	14	14.0	0
1c	14	13	13.5	−1
2a	09	10	9.5	+1
2b	9.5	10	9.75	+0.5
2c	09	09	9.0	0
3a	3.4	4.0	3.7	+0.6
3b	3.4	4.0	3.7	+0.6
3c	3.4	4.0	3.7	+0.6
4a	5.0	5.0	5.0	0
4b	5.0	6.0	5.5	+1
4c	5.0	6.0	5.5	+1
5a	15	13	14	−2
5b	12	13	12.5	+1
5c	15	14	14.5	−1
6a	26	25	25.5	−1
6b	24	23	23.5	−1
6c	26	24	25	−2
7a	16	18	17	+2
7b	18	18	18	0
7c	19	17	18	−2
				mean difference −0.13 (cm H_2O)

end-exhalation. And, third, because no extra equipment is required to perform the manoeuvre the cost would be less.

Conclusion

Employing the expiratory hold function of the Siemens 900C ventilator when equipped with a low-compressible-volume circuit may prove to be an accurate, rapid, and cost effective method for the clinical measurement of $PEEP_i$.

ACKNOWLEDGMENTS

We thank Janet Lee Haines for computer expertise and Pamela M Merrick BSN for statistical analysis.

REFERENCES

1. Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction. Am Rev Respir Dis 1982;126:166-170.
2. MacIntyre NR. Intrinsic positive end-expiratory pressure. In: Fulkerson WJ, MacIntyre NR, editors. Complications of mechanical ventilation. Prob Respir Care. Philadelphia: JB Lippincott, 1991:(4):44-51.
3. Grootendorst AF, Lugtigheid G, Jan van der Weygert E. Error in ventilator measurements of intrinsic PEEP: cause and remedy. Respir Care 1993;38:348-350.
4. Servo Ventilator 900C operating manual, 2nd edition. Danvers MA: Siemens Medical Systems, September 1982.
5. Bland M. An introduction to medical statistics. Oxford: Oxford University Press, 1987.

Bezold-Jarisch Reflex—An Indication for Closed System Suctioning: A Case Report

Tai-Shion Lee MD and Yaw Wu MD

Introduction

Patients in whom the Bezold-Jarisch reflex (an inhibitory reflex originating in the heart) is elicited are vulnerable to develop bradycardia and hypotension. In mechanically ventilated patients, interruption of the patient-ventilator circuit by disconnection of the endotracheal tube from the ventilator for suction may trigger this reflex. We present a subject in whom repeated episodes of bradycardia and hypotension, probably due to Bezold-Jarisch reflex, were successfully prevented with the use of a closed tracheal suction system.

Conventional open endotracheal suctioning with a disposable catheter requires that the patient be disconnected from the ventilator. It has been reported to be associated with some complications, including loss of PEEP, oxygen desaturation, cardiac dysrhythmias and arrest, and respiratory infection.[1-3] Closed airway suction systems were introduced to overcome these problems. The major difference is that they provide a method of intermittent suctioning without disruption of the patient-ventilator circuit. Even though their advantages and disadvantages remain controversial, the overall clinical responses seem to be favorable.[1-5]

Case Summary

A 55-year-old man was admitted to the surgical intensive care unit following laparotomy for a perforated duodenal ulcer. He was a heavy smoker with a long history of chronic obstructive pulmonary disease. His medications included bronchodilators, diuretics, and digoxin. He had been found to have lung cancer and had been on chemotherapy for 2 months. A Graham-Steele closure was performed during the operation (ie, the perforation was plugged with omentum sutured in place). He was mechanically ventilated and received parenteral nutritional support postoperatively. Initial ventilator settings were F_{IO_2} 0.4, tidal volume (V_T) 800 mL, and assist-control rate (f) 12/min. The peak inspiratory airway pressure (PIP) was 32 cm H_2O and heart rate was 98/min. There was no evidence of dysrhythmia or circulatory instability, and blood gas values were initially acceptable. He was on continuous pulse-oximeter and end-tidal CO_2 monitoring. Two days later, he developed bilateral infiltration and pleural effusion on the left. Deterioration in his condition suggested ARDS. Because of persistent hypoxemia and hypercapnia, the ventilator settings were changed to V_T 900 mL and PEEP 15 cm H_2O. The PIP at this time was 58 cm H_2O. Seventy-two hours later, he developed a new problem—each attempt at suctioning the airway was associated with profound bradycardia followed by hypotension. This bradycardia (30-40/min), sometimes with premature ventricular contractions (PVCs), occurred about 3-10 seconds after disconnection of the tube (Table 1), even before suctioning or any change in oxygen saturation as indicated by pulse oximetry. It could usually be reversed by immediate reconnection to the ventilator or administration of intravenous atropine. The cardiologist consulted suggested that the bradycardia and hypotension were probably triggered by a Bezold-Jarisch reflex. Because of an earlier, almost-fatal suctioning episode with a patient thought to exhibit the Bezold-Jarisch reflex, we decided to use a closed tracheal suction system (Trach Care®, Ballard Medical

Dr Lee is Associate Professor and Co-Director of Surgical ICU, and Dr Wu is Assistant Professor—Department of Anesthesiology, Harbor-UCLA Medical Center, Torrance, California.

Reprints: Tai-Shion Lee MD, Department of Anesthesiology, Harbor-UCLA Medical Center, Torrance CA 90509.

Products, Midvale UT). After institution of the closed system, no more bradycardia occurred in spite of repeated suctioning of the airway. The patient was eventually weaned from mechanical ventilation and extubated 18 days after surgery. By that time, the reflex bradycardia had disappeared spontaneously.

Table 1. Heart Rate Changes with Open or Closed Airway Suction Method

	Before Suction	During Suctioning	
		Open	Closed
Heart rate/min	90-100	30-40	95-130

Discussion

In the ICU, sudden onset of bradycardia can occur when neural, hormonal, metabolic, or hemodynamic factors in or near the sinus node cause it to slow its intrinsic pacemaker rate. Certain pharmacologic agents (including beta-blockers, morphine, digitalis, quinidine, clonidine, xylocaine, and calcium-channel blocking agents) can induce bradycardia that does not usually present abruptly unless toxic doses are given. Many pathologic conditions may also produce bradycardia (for example, acute myocardial ischemia or infarction, degenerative or inflammatory disease of the sinus node, hypothyroidism, hypothermia, increased intracranial pressure, high spinal anesthesia or cervical spine injury, and hypoxemia or hypoxia). On the other hand, bradycardia is commonly triggered by vagal reflexes or maneuvers such as carotid sinus stimulation, increase in ocular pressure, vomiting, valsalva maneuver, vasodepressor syncope, and left ventricular reflexes.[6-10] It was easy to rule out many of the listed causes in the case presented, with the exception of vagal reflex and hypoxemia. In the present case, we observed only episodes of sinus bradycardia, with or without PVCs, and no evidence of heart block. The follow-up electrocardiogram showed normal sinus rhythm and no signs of ischemia or infarction. The patient was not on any medications that could cause bradycardia except digoxin, and the most recent serum digoxin level had been 1.2 ng/mL (toxic level is > 2.0 ng/mL), and the bradycardia was of abrupt onset and transient. Hypoxemia could have been the cause, but this was unlikely without obvious oxygen desaturation; even though there could have been some delay in the appearance of desaturation on pulse oximetry, bradycardia developed almost immediately after disconnection of the tube and was reversed rapidly with atropine. The vagal reflex triggered by tracheal irritation due to manipulation of the tube could not be completely ruled out, despite the fact that suctioning of the trachea itself did not appear to provoke bradycardia.

Bezold-Jarisch reflex is an inhibitory reflex originating in the heart that causes bradycardia, vasodilation, and hypotension. Its importance to the pathophysiology of major cardiovascular derangements has been recently reappreciated.[8-10] The cardiac sensory receptors, which are principally distributed in the inferoposterior wall of the left ventricle, can be activated chemically or mechanically. Besides chemical or pharmacologic stimulation, similar to arterial baroreflex through the carotid sinus, the cardiac mechanoreflex can be triggered by excessive activation of cardiac mechanoreceptors. Cardiac distention and stretching or vigorous, forceful, and rapid systolic contraction can trigger activity that is relayed to the medulla by nonmyelineated afferent fibers in the vagus nerves and elicits a reflex. The resultant increases in parasympathetic and inhibition of sympathetic activities lead to bradycardia, vasodilation, and hypotension.[8-10] These receptors do not respond directly to hypoxia and hypercapnia.[11] This reflex has been reported to occur during ventricular syncope, inferoposterior myocardial ischemia and infarction,[12] coronary arteriography,[13] exertional syncope in aortic stenosis,[8] vasovagal syncope,[9] neurohumoral excitation in chronic heart failure,[14] and administration of digitalis.[15] In severe cases, cardiac arrest can occur.[8-10] Atropine is the drug of choice in this situation because it antagonizes not only the bradycardia but also the reflex cholinergic vasodilation.[8]

In this case, the etiology of the bradycardia and hypotension was determined by exclusion. We postulate that the mechanism can be explained by the Bezold-Jarisch reflex. In mechanically ventilated patients, particularly in cases with high PIP and PEEP, sudden interruption and release of positive airway pressure by disconnection from the ventilator for suctioning may abruptly decrease the intrathoracic pressure and promptly increase the venous return and central blood volume. This rapid volume expansion with an increase in cardiac filling pressure and cardiac size stimulates the cardiac receptors and elicits a reflex increase of parasympa-

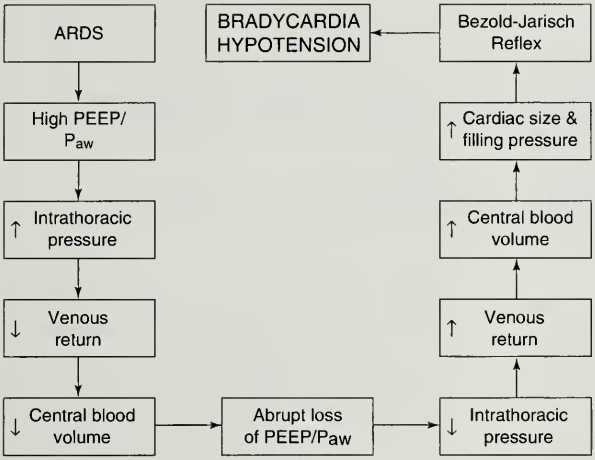


Fig. 1. Schema of the postulated mechanism for Bezold-Jarisch reflex in mechanically ventilated patients.

thetic activity and withdrawal of sympathetic tone in susceptible patients (Fig. 1). Further studies with echocardiogram may be useful to confirm this hypothesis. Negative pressure caused by suctioning may exaggerate the condition. The rapid onset (even before suctioning and desaturation) and the rapid response to atropine suggest that hypoxemia is not the primary cause of bradycardia. The closed tracheal suction system provides a method of intermittent suctioning without complete disruption of the patient-ventilator circuit and, thus, avoids triggering the Bezold-Jarisch reflex. We believe that it may be a special indication for this suction system in these patients both in the ICU and in the operating room.

REFERENCES

1. Ritz R, Scott LR, Coyle MB, Pierson DJ. Contamination of a multiple-use suction catheter in a closed-circuit system compared to contamination of a disposable, single-use suction catheter. Respir Care 1986;31(11):1086-1091.
2. Craig KC, Benson MS, Pierson DJ. Prevention of arterial oxygen desaturation during closed-airway endotracheal suction: effect of ventilator mode. Respir Care 1984; 29(10):1013-1018.
3. Bodai BI, Briggs SW III, Goldstein M, McLaughlin G, Haas A. Evaluation of the ability of the Neo_2Safe valve to minimize desaturation in neonates during suctioning. Respir Care 1989;34(5):355-359.
4. Deppe SA, Kelly JW, Thoi LL, Chudy JH, Longfield RN, Ducey JP, Truwit CL, Antopol MR. Incidence of colonization, nosocomial pneumonia, and mortality in critically ill patients using a Trach Care® closed-suction system versus an open-suction system: prospective, randomized study. Crit Care Med 1990;18(12):1389-1393.
5. Guthrie MM, Off DG. Closed-airway suctioning (letter). Respir Care 1985;30(5):355-358.
6. Barron KW, Bishop VS. Roles of right versus left vagal sensory nerves in cardiopulmonary reflexes of conscious dogs. Am J Physiol 1985;249(3, Part 2):R301-R307.
7. Fullerton DA, St Cyr JA, Clarke DR, Campbell DN, Toews WH, See WM. Bezold-Jarisch reflex in postoperative pediatric cardiac surgical patients. Ann Thorac Surg 1991;52(3):534-536.
8. Mark AL. The Bezold-Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. J Am Coll Cardiol 1983;1(1):90-102.
9. Abboud FM. Ventricular syncope: is the heart a sensory organ? N Engl J Med 1989;320(6):390-392.
10. Linzer M. Syncope: 1991 (editorial). Am J Med 1991; 90(1):1-5.
11. Mark AL, Abboud FM, Heistad DD, Schmid PG, Johannsen UJ. Evidence against the presence of ventricular chemoreceptors activated by hypoxia and hypercapnia. Am J Physiol 1974;227(1):178-182.
12. Kezdi P, Kordenat RK, Misra SN. Reflex inhibitory effects of vagal afferents in experimental myocardial infarction. Am J Cardiol 1974;33(7):853-860.
13. Perez-Gomez F, Garcia-Aguado A. Origin of ventricular reflexes caused by coronary arteriography. Br Heart J 1977;39(9):967-973.
14. Zucker IH, Share L, Gilmore JP. Renal effects of left atrial distension in dogs with chronic congestive heart failure. Am J Physiol 1979;236(4):554-560.
15. Thames MD, Waickman LA, Abboud FM. Sensitization of cardiac receptors (vagal afferents) by intracoronary acetylstrophanthidin. Am J Physiol 1980;239(5):H628-H635.

Idiopathic Vocal Cord Paralysis in a Newborn Infant: A Case Report

Katherine A Douglas BEd RCP RRT and Ramalinga Polamreddy MD

Introduction

Vocal cord paralysis in a newborn infant may manifest clinically with a variety of symptoms. Inspiratory stridor, suggesting extrathoracic upper airway obstruction, may be the result of either an anatomic or a functional lesion such as vocal cord paralysis (VCP). Examination of the larynx with a fiberoptic bronchoscope is necessary to determine the cause of stridor.

In at least one third of patients, the etiology of VCP remains unknown.[1-3] We report a case of a prematurely born infant who developed inspiratory stridor shortly after birth.

Case Summary

A 2.07-kg boy was delivered at a community hospital by spontaneous vaginal vertex delivery at 33-weeks gestation. The amniotic fluid was clear, and there was no evidence of any complications associated with the delivery. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The infant had mild respiratory distress as evidenced by nasal flaring, chest retractions, and grunting. He was placed in an incubator with the fraction of inspired oxygen (F_{IO_2}) 0.30-0.35. The infant's oxyhemoglobin saturation was monitored by pulse oximetry (S_{pO_2}) and F_{IO_2} adjusted to maintain $S_{pO_2} > 90\%$. Initial blood count and glucose levels were normal. The referring physician reported that this was an infant of 33-weeks gestation by examination who probably had respiratory distress syndrome (RDS) or respiratory distress secondary to sepsis. However, according to this physician, the chest radiograph obtained shortly after birth did not support his initial impression.

The first documentation of inspiratory stridor in this patient was made by our transport team when they arrived at the community hospital to initiate this patient's transfer to our center. The baby was 2 hours of age and breathing supplemental oxygen (F_{IO_2} 0.27). He had mild intercostal, subcostal, and substernal retractions. Breath sounds were clear bilaterally and suggested adequate air exchange. The baby was pink and alert, and was stridorous only with crying or agitation. An oxygen challenge test (hyperoxia test) was performed to rule out congenital, cyanotic heart disease (CCHD). The transport team administered F_{IO_2} 1.0, and the transcutaneous oxygen tension (P_{tcO_2}) rose to more than 200 torr. With this test, our transport team felt that a serious cyanotic heart defect was unlikely. A subsequent blood gas analysis done in F_{IO_2} 0.21 (pH, P_{aO_2}, and P_{aCO_2}) yielded normal values. Transport of the infant was uneventful.

Upon arrival at our hospital, the baby continued to have mild respiratory distress and intermittent inspiratory stridor. Over the next 24 hours, desaturation episodes ($S_{pO_2} < 90\%$) associated with apnea or with apnea and bradycardia (heart rate < 80 beats/min) during feeding made it necessary to discontinue oral feedings and support the patient's nutrition entirely with parenteral fluids. Theophylline therapy (standard treatment for apnea of prematurity) and nasal oxygen at 0.5 L/min were begun. We were able to reduce the baby's oxygen to room air again over the next few hours.

Because of the recurring stridor, an upper airway examination by fiberoptic bronchoscopy was done under local anesthesia on the following day (the in-

Ms Douglas is a Clinical Specialist in the Department of Respiratory Care and Dr Polamreddy is Associate Professor of Medicine, Medical College of Toledo, and Associate Director of Pediatric Pulmonary Medicine—The Toledo Hospital, Toledo, Ohio.

fant's second day of life). Bilateral vocal cord paralysis and normal anatomy of the glottis and trachea were seen. Because central nervous system (CNS) abnormalities and other congenital anomalies are known to be associated with VCP, a magnetic resonance imaging (MRI) study was done. A pneumogram was done to determine whether the baby was experiencing obstructive vs central apnea. The MRI was negative for congenital anomalies and structural abnormalities. The pneumogram showed multiple episodes of both obstructive and central apnea, fluctuations in heart rate without true bradycardia (80-100 beats/min), and desaturation ($S_{pO_2} < 80\%$). Following the upper-airway examination, gavage feedings were started. By the end of the first week of life, the baby's inspiratory stridor was no longer intermittent but was unabated even when he was quiet. All laboratory values, including blood gases, remained within normal limits. During this time we began to alternate gavage and nipple feedings.

Bronchoscopy was repeated on Day 13. At this time, we noted that the vocal cords moved with coughing. Normally, the vocal cords adduct (close the glottis by meeting in the midline) during swallowing.[4] In our patient, some adduction was noted, so we decided to try to use nipple feedings exclusively, watching the baby closely for signs of choking or episodes of desaturation. He did well initially, but at 3 weeks of age began to show signs of tiring and had some periods of desaturation with feedings. Apnea and bradycardia events became more frequent, and gavage feedings were again alternated with nipple feedings. A third bronchoscopy revealed little movement of the vocal cords. Large arytenoid folds seemed to contribute to the upper airway obstruction and stridor. When the vocal cords are functioning properly, they abduct away from the midline during inspiration.[5] However, when our patient inspired, the large arytenoid folds were sucked into the airway between the vocal cords producing partial airway obstruction and the classic sound—stridor. Our impressions, at this time, were that this infant had bilateral vocal cord paresis and functional arytenoid malacia. Because it was apparent that gavage feedings would be necessary for some time, and, in anticipation of the infant's discharge, the infant had a gastrostomy tube inserted at 36 days of age. His surgery and postoperative course were uneventful, and gastrostomy feedings were initiated on the second postoperative day. This infant had no more episodes of desaturation, bradycardia, or apnea and continued to gain weight. A final pneumogram prior to discharge was normal.

The infant was discharged home on a cardiorespiratory monitor, gastrostomy gavage feedings, and theophylline therapy. During a subsequent bronchoscopy at 5 months of age, vocal cord movement remained minimal. There have been no alarms from the cardiorespiratory monitor. A subsequent pneumogram was normal, and the child has been started again on oral feedings. His stridor is minimal and only apparent when he is excited. He is scheduled for another flexible bronchoscopy at age 6 months.

Discussion

Abnormal breathing sounds (eg, audible stridor) in newborns may herald any number of serious conditions. Grunting, stridor, and high-pitched crying may each suggest a number of different disorders. Respiratory distress in newborn infants is not synonymous with RDS (Table 1).[6] Therefore, those who care for newborn infants must not only correctly identify these various sounds and be aware of the diversity of potential causes of newborn respiratory distress but must also be prepared to choose and administer the appropriate therapy.

Flexible Bronchoscopy

Stridor is a sound produced by turbulent airflow. It may be the result of a partial obstruction in the airway or compression of the soft portions of the airway.[7] Prior to the availability of a flexible bronchoscope for infants, stridor in newborns was often assumed to be secondary to laryngomalacia.[2,8] Given these limitations—lack of equipment to examine the very small airway and the need for general anesthesia with rigid bronchoscopic examination—direct visualization of the upper airway of infants was rarely done. Additionally the rigid bronchoscope permitted examination of only the static rather than the dynamic properties of the upper airway. However, in recent years the relative ease of upper airway examination by flexible bronchoscopy with local anesthesia has enabled us to ascertain the cause(s) of stridor under dynamic conditions. We are now able to see how the various structures be-

Table 1. Differential Diagnosis of Respiratory Distress in a Newborn Infant

Pulmonary and Airway Etiology
Developmental
Choanal atresia
Laryngeal web, cyst, vocal cord paralysis
Laryngotracheomalacia
Cystic adenomatoid malformation
Congenital lobar emphysema
Congenital pulmonary hypoplasia (Potter's syndrome)
Respiratory distress syndrome
Tracheal stenosis
Infections
Congenital viral or bacterial pneumonia
Neonatal sepsis—early onset
Aspiration of meconium, blood, or amniotic fluid
Pulmonary air leak
Other
Transient tachypnea of the newborn
Chylothorax
Pulmonary hemorrhage
Congenital lymphangiectasis
Nonpulmonary Etiology
Congenital heart disease
Tracheoesophageal fistula
Diaphragmatic hernia
Neuromuscular disorders
Maternal medication
Central nervous system pathology

have during a normal breath. Because general anesthesia is not necessary, bronchoscopy can be performed at the infant's bedside, eliminating the risks and expense associated with transporting the patients to the operating room. Until the airway of a stridorous pediatric patient is visually examined, the diagnosis is presumptive.[7,9]

Incidence, Treatment, & Resolution of VCP

A decade ago, Richardson and Cotton[7] stated that vocal cord paralysis is the second most common laryngeal anomaly in newborn infants.The incidence of VCP in samples of infants with laryngeal anomalies varies from 1.5%[10] to 23%.[11] Table 2 provides a brief summary of some reviews of VCP in recent literature and their pertinent findings.[1-3,8,9,12,13] The mechanism and degree of respiratory distress resulting from VCP is also highly variable. If the paralysis is bilateral rather than unilateral, the child is more often symptomatic and is, therefore, generally diagnosed earlier.[3,5,9] In addition to the feeding problems with attendant risk of aspiration, phonation may be affected in patients, as well.[5]

Treatment for VCP covers a broad spectrum of care from a conservative "wait and watch" approach, which may suffice in most cases of unilateral paralysis, to tracheotomy for those infants and children with serious respiratory compromise associated with unilateral or bilateral paralysis.[2,5] Tracheotomy should be considered if growth is not optimal or if there is evidence of impending pulmonary hypertension secondary to the upper airway obstruction.[14] Resolution of idiopathic VCP generally occurs spontaneously. However, the time frame for resolution cannot be predicted and, in the studies cited in Table 2, varied from months to years.[1-3]

No deaths were reported among those patients identified with idiopathic VCP in the reviews in Table 2.[1-3] With careful observation and management, it is unlikely that infants with VCP will die from their paralysis.[12] However, the associated morbidity includes prolonged hospital stay, the need for more extensive follow-up,[5,12] and the attendant increased cost and stress to the family.

The Differential Diagnosis

The complicating factor in the case that we report was the infant's prematurity. Although the baby had mild respiratory distress shortly after birth, the diagnosis of RDS was not supported by the chest radiograph. Two other diagnoses known to precipitate respiratory distress in a newborn are sepsis and CCHD. Sepsis is treated presumptively with antibiotics pending results of a blood culture. CCHD may be ruled out quickly using an oxygen challenge test, as was done with our patient. By the time this infant arrived at our center, his condition was so improved that an anatomic lesion (eg, a laryngeal web) was not seriously considered in the differential diagnosis. The first bronchoscopy confirmed the absence of any such lesion. Inherited VCP has been described,[15] but there was no family history to suggest this etiology in this case.

In Summary

Stridor must first be accurately identified by the infant's caregivers. Newborn infants who present

Table 2. Studies Reporting Vocal Cord Paralysis (VCP) in Children: Incidence and Outcome

First Author	Cases of VCP	Subjects' Ages	Cases of Idiopathic VCP	Major Findings
Swift[1]	22 in 11 years	0-36 months	7	Recovery was complete in all cases.
Gentile[2]	22 in 13 years	0-3 months	6	11/12 patients with bilateral VCP required tracheotomy.
Rosin[3]	51 in 11 years	0-6 months	20	Patients with bilateral VCP were diagnosed earlier than those with unilateral VCP.
				10/29 patients with bilateral VCP did not require tracheotomy.
Chaten[8]	9 in 18 months	17 days-5.5 years	0	6/7 patients with bilateral VCP required tracheotomy.
				VCP may be the cause of extubation failure in pediatric patients.
Holinger[9]	17 in 4 years	0-2.5 years	0	All cases of VCP had underlying neurologic disorder.
				5/14 patients with bilateral VCP required tracheotomy.
				58/219 patients had been misdiagnosed prior to bronchoscopy.
Tucker[12]	30 in 10 years	0-5 years	0	Tracheotomy required in all cases of bilateral VCP and in 6/8 patients with unilateral VCP.
				VCP is uncommon but often disabling in children.
Davis[13]	3 in 7 years	16-27 days	0	Studied 106 patients who had patent ductus ligation.
				3/68 patients who had suture ligation developed unilateral VCP compared to none who had surgical-clip closure.

with or develop stridor require direct visualization of the upper airway before a definitive diagnosis can be made and unnecessary treatment avoided. In cases of bilateral VCP, tracheotomy may be necessary. Irrespective of the cause, infants with VCP must be followed closely after discharge from the hospital to avoid catastrophic events and to detect subtle complications such as retarded growth and development and pulmonary hypertension. Recovery from idiopathic VCP is good in most cases affecting infants and children. However, time to resolution is highly variable and may not occur for months or years.[1,2]

ACKNOWLEDGMENTS

We extend a special thanks to Dr Harold Stevens for his manuscript review and suggestions. Dr Stevens is a gracious mentor, educator, and advocate for respiratory care students and professionals.

REFERENCES

1. Swift AC, Rogers J. Vocal cord paralysis in children. J Laryngol Otol 1987;101(2):169-171.
2. Gentile RD, Miller RH, Woodson GE. Vocal cord paralysis in children 1 year of age and younger. Ann Otol Rhinol Laryngol 1986;95(6, Part 1):622-625.
3. Rosin DF, Handler SD, Potsic WP, Wetmore RF, Tom LWC. Vocal cord paralysis in children. Laryngoscope 1990;100(11):1174-1179.
4. Orenstein DM, Orenstein SR. Gastroesophageal reflux and dysfunctional swallowing. In: Loughlin GM, Eigen H, eds. Respiratory disease in children: diagnosis and management. Baltimore: Williams & Wilkins, 1994: 563-586.
5. Handler SD. The larynx. In: Rudolph AM, ed. Pediatrics, 18th edition. East Norwalk CT: Appleton & Lange, 1987:883-898.
6. Stern L, ed. Diagnosis and management of respiratory disorders in the newborn. Menlo Park CA: Addison-Wesley, 1983:5.

7. Richardson MA, Cotton RT. Anatomic abnormalities of the pediatric airway. Pediatr Clin North Am 1984;31(4): 821-834.
8. Chaten FC, Lucking SE, Young ES, Mickell JJ. Stridor: intracranial pathology causing postextubation vocal cord paralysis. Pediatrics 1991;87(1):39-43.
9. Holinger LD. Etiology of stridor in the neonate, infant and child. Ann Otol Rhinol Laryngol 1980;89(5, Part 1): 397-400.
10. MacKenzie IJ, Kerr AIG, Cowan DL. A review of endoscopies of the respiratory tract and oesophagus in a children's hospital. Health Bulletin (Edinburgh) 1984;42:78-80.
11. Cohen SR, Eavey RD, Desmond MS, May BC. Endoscopy and tracheotomy in the neonatal period: a 10-year review, 1967-1976. Ann Otol Rhinol Laryngol 1977; 86(5,Part 1):577-583.
12. Tucker HM. Vocal cord paralysis in small children: principles in management. Ann Otol Rhinol Laryngol 1986; 95(6, Part 1):618-621.
13. Davis JT, Baciewicz FA, Suriyapa S, Vauthy P, Polamreddy R, Barnett B. Vocal cord paralysis in premature infants undergoing ductal closure. Ann Thorac Surg 1988;46(2):214-215.
14. Noonan JA. Cor pulmonale. In: Cherniak V, ed. Kendig's disorders of the respiratory tract in children, 5th ed. Philadelphia: WB Saunders, 1990:683-692.
15. Grundfast KM, Milmoe G. Congenital hereditary bilateral abductor vocal cord paralysis. Ann Otol Rhinol Laryngol 1982;91(6, Part 2):564-566.

AARC

American Association for Respiratory Care
40th Annual Convention and Exhibition
December 10-13, 1994 • Las Vegas, Nevada

Cerebral Arterial Gas Embolism: A Review and Update

Vaughn Nelson MD, Eva Nelson MD, and A Joseph Layon MD

I. Introduction
II. Pathogenesis
III. Making the Diagnosis
A. Signs & Symptoms
B. Differential Diagnosis
C. Pathophysiology
IV. Issues in the Treatment of CAGE
A. Immediate Treatment
B. In-Transit Treatment
C. In-Hospital Treatment
V. In Summary

Introduction

Cerebral arterial gas embolism (CAGE) has been implicated in transient, as well as permanent, neurologic deficits in patients undergoing coronary artery bypass grafting,[1,2] neurosurgical procedures in the sitting position,[3] cesarean section (venous air embolism),[4] transthoracic lung biopsy,[1,5,6] and open intra-abdominal procedures.[2,7] Other scenarios in which CAGE occurs include diving accidents,[8] traumatic lung injury, barotrauma that sometimes results from mechanical ventilation in patients with the adult respiratory distress syndrome (ARDS), and rather unusual events that are either accidently or intentionally induced during sexual frolicking.[9,10] In this review, we explore the pathogenesis, signs, symptoms, diagnosis, pathophysiology, and therapeutic interventions for CAGE. When animal studies suggest intriguing interventions that require further evaluation in humans, we so note.

Cerebral arterial gas embolism is defined as gas that passes into the cerebral arterial circulation from any of a variety of causes. For example, CAGE may result from direct entry of air into the arterial circulation as may occur in an open-cardiac procedure. Alternatively, it may occur via paradoxical air embolism (PAE) from the venous circulation. The clinical syndrome seen in a specific patient depends upon the route of air movement as well as its final resting place.

Pathogenesis

Arterial gas embolism may be the result of dysbarism, a term describing the sequelae of altered environmental pressures. Dysbarism commonly affects divers and compressed-air workers who are exposed to higher ambient pressures and can also occur in fliers and astronauts who experience sud-

Dr Vaughn Nelson is Senior Resident and Dr Eva Nelson is Chief Resident, Department of Anesthesiology, and Dr Layon is Associate Professor in the Departments of Anesthesiology and Medicine—University of Florida College of Medicine, Gainesville, Florida.

An abbreviated version of this paper will appear in *Pulmonary and Critical Care Update* published by the American College of Chest Physicians in August (Vol 10, Lesson 1).

Reprints: A Joseph Layon MD, Univeristy of Florida College of Medicine, PO Box 100254, 1600 SW Archer Rd, Gainesville FL 32610-0254.

den subatmospheric pressures.[11] Two forms of dysbarism exist: barotrauma and decompression sickness (DCS). Barotrauma and CAGE do not depend upon the depth or the duration of the dive. Both can result from breath-holding during ascent following a compressed-air dive from depths of 10 feet or less.[12] Even after ascent from this minimal depth, pressure around the thorax decreases and intrathoracic volume increases in direct proportion to the decrease in pressure, in compliance with Boyle's law. If the lungs are not adequately vented (ie, forced exhalation), pressure and volume reach a critical point, alveolar rupture occurs, and air may dissect into the pulmonary capillary system,[13] the mediastinum, and the pericardium.

Air in the pulmonary vasculature may distribute to the arterial system, given the proper conditions (see below); the resulting clinical syndrome depends upon the destination of the air.[14] When the subject is in the horizontal position, such as intraoperatively, air commonly distributes to the coronary arteries and peripherally. In the vertical position, such as during ascent from scuba diving, air distributes to the cerebral arteries. The intracranial vessels to which air most commonly distributes are the anterior and middle cerebral arteries.[11] When barium sulfate and celloidin were injected into the internal carotid arteries of 14 dogs, emboli were widely distributed throughout the cerebral circulation.[15] For instance, emboli were present in areas supplied by the ipsilateral middle cerebral artery in all of the animals. Ten of 14 had emboli present in both the ipsilateral anterior cerebral distribution and the ipsilateral posterior cerebral distribution. Contralateral emboli were noted in 11 of 14 dogs and 9 of 14 had embolization in the region supplied by the anterior cerebral artery.[15] Thus, this study illustrates the multifocal nature of CAGE.

Cerebral arterial gas embolism must be distinguished from DCS, which is another form of dysbarism and a complication of scuba diving. Decompression sickness, also known as "the bends" or Caisson's disease, occurs as the inert gas, nitrogen, comes out of solution during ascent from depth. Nitrogen normally passes from tissues to the blood and is carried to the lungs, where it is exhaled. If the depth and duration of the dive are extensive enough to supersaturate tissues with nitrogen, then during a rapid ascent the gas comes out of solution and cannot be cleared from the tissues quickly enough.[13] The result is thought to be formation of gas bubbles in the tissues and microvasculature, rather than obstruction of larger blood vessels by intravascular bubbles. If the tissue is noncompliant, bubble formation results in compression of adjacent structures, such as nerves, blood vessels, and lymphatics.[16] Because nitrogen is fat soluble, it dissolves in myelin. Therefore, intramyelin bubble formation may result in disruption of the neural sheath.[16] As explained previously, impaired arterial supply and venous outflow may result from compression of vessels. Damage to local tissue, including the endothelium, results in induction of platelet aggregation, activation of the coagulation cascade and thrombus formation, and neutrophil accumulation, all of which further compromise the microcirculation.[16]

Two clinical presentations of DCS are possible: Type I presents primarily with joint pain and pruritus, whereas Type II DCS involves neurologic deficits. Type II DCS commonly affects the posterior and lateral columns of the spinal cord (white matter) without damage to the grey matter.[17] The nature of the damage is usually multifocal. When Type II DCS affects the brain, it is termed cerebral DCS. Although cerebral DCS is often confused with CAGE, the mechanism of injury is different, as is the morbidity and mortality. Methods of distinction between CAGE and cerebral DCS are discussed below and are summarized in Table 1.

Several cases of air embolism have been noted in patients with ARDS. Marini and Culver[18] and Morris et al[19] have each reported 2 cases in which sudden neurologic events were seen in patients with ARDS in the setting of barotrauma-induced intraparenchymal air collections. In ARDS, the retractive tendencies of inflamed pulmonary parenchyma may cause the tethering open of vessels, resulting in air entry.[18]

In summary, CAGE results when air is introduced into the arterial system either directly or via paradoxical movement of venous air. DCS is thought to result from bubble formation in the venous system and body tissues, although an inflammatory process may intervene after the gas comes out of solution, worsening the neurologic lesion.

Table 1. Differentiating Cerebral Arterial Gas Embolism (CAGE) from Decompression Sickness (DCS)

	CAGE	Cerebral DCS
Pathogenesis		
Operative occurrence	Yes	No
Scuba diving occurrence	Yes	Yes
Via paradoxical air embolism (PAE)	Yes	Probably not
Signs/Symptoms		
Rapid onset (minutes)	Usually	Occasionally
Loss of consciousness	Yes (≈ 40%)	Uncommon
Stupor	Yes	Yes
Focal Neurological Signs		
≤ 10 min after surfacing	Yes	No
> 10 min after surfacing	Yes	Yes
Headache	Less prominent	More prominent
Rash, musculoskeletal pain	Less likely	More likely
Historical Data		
Emergency ascent	Yes	No
Normal ascent with long decompression time	No	Yes

Air may enter the arterial circulation either directly, as mentioned earlier, or after passage through the venous system. In the latter case, it is known as paradoxical arterial embolism (PAE). The most common portal of entry for PAE is a patent foramen ovale. From an autopsy study of 965 normal hearts, Hagen et al[20] reported this cardiac abnormality had an incidence in the general population of 27.3%. If a bolus of air lodges in the pulmonary outflow tract, elevated right heart pressures may occur, causing a right-to-left shunt through the now-patent foramen ovale. As a result, air can traverse the foramen ovale and pass into the arterial circulation.[2] An intriguing paper by Black and colleagues[21] recently showed, in a pig model, that right atrial pressure only had to exceed left atrial pressure during a *portion* of the cardiac cycle for PAE to occur.

Paradoxic arterial embolism may also occur via passage of air bubbles through the pulmonary vasculature and into the arterial circulation. The lungs can normally filter air bubbles as large as 22 μ when a small volume is infused slowly. However, a bolus of 30 mL of air injected into the central venous circulation of a canine model resulted in passage of air into the arterial circulation.[22] Butler and Hills[22] detected air in the carotid arteries of dogs via transcranial Doppler aortography after the venous injection of air at a dose of $0.3 \cdot kg^{-1} \cdot min^{-1}$. Lag time from venous injection to appearance in the arterial circulation ranged from 12 to 90 minutes. Thus, symptoms consistent with CAGE may be noted in both arterial gas embolization, venous air embolization with paradoxical movement of gas, and Type II DCS. It is frequently impossible to differentiate except on the basis of the clinical scenario that preceded the event.

Making the Diagnosis

Signs & Symptoms

Cerebral arterial gas embolism is most often a disease of rapid onset. In a study by Francis et al,[14] 56% of cases of CAGE secondary to scuba-diving accidents became symptomatic within 10 minutes of returning to the surface. Dick and Massey[23] showed that 27 of 39 divers (69%) with CAGE experienced symptoms upon surfacing, and 82% had symptoms within 10 minutes. Only rarely did CAGE present more than 6 hours after surfacing. In contrast, none of the divers with DCS had symptoms upon surfacing, and only 62% had symptoms within the first 6 hours thereafter.[23] However, the latency of cerebral DCS is occasionally quite short—less than 10 minutes has been reported.[14] Therefore the time to onset of symptoms, while helpful, is not a totally reliable method of differentiation between cerebral DCS and CAGE.

Common signs and symptoms of CAGE include unconsciousness in up to 40%;[24] stupor in 7% to 20%;[23] sensory loss in 20%;[24] motor deficit in 20%;[24] paraplegia or paresis in 10%;[24] seizures in 4% to 8%;[23] visual disturbances in 8% to 23%;[23] severe headache in 23%;[23] and chest pain in 10%.[24] Other signs of CAGE on physical examination include dyspnea, tachypnea and other variations of respiratory pattern, dysrhythmias, and circulatory insufficiency.[25] Cardiorespiratory arrest and death occur immediately in approximately 7% of cases of CAGE secondary to diving accidents.[26]

Differential Diagnosis

The initial diagnosis of CAGE is usually based solely on history and physical examination[27] and is often one of exclusion; additionally, CAGE is fre-

quently associated with pneumomediastinum or pneumothorax. In scuba divers, the primary factor that differentiates CAGE from Type II DCS is the length of time from the incident to the onset of signs and symptoms. However, as mentioned earlier, this is not always reliable in differentiating between the two. Differentiation may have to be based on circumstances surrounding the event. For instance, diver inexperience, panic, emergency ascent, and/or pre-existing acute or chronic pulmonary problems may be associated with CAGE.[14] In contrast, depth and duration of the dive, the number of consecutive dives, physical condition, age, weight, ethanol consumption, and the strenuousness of work performed while at depth may contribute to DCS.

Venous air embolism should be part of the differential diagnosis because of the potential for PAE. Hoffman and colleagues[28] described their study in which air was introduced via the femoral vein at 0.5 mL/s in dogs for increasing amounts of time. If air was injected for 10 to 15 seconds, the heart sounds developed a metallic quality. By 20 to 25 seconds, the heart sounds became drum-like, and by 30 to 40 seconds became like a "galloping horse on a wooden bridge." After 50 to 60 seconds of injection, the heart sounds became "mill-wheel like."[28] Unfortunately, changes in heart sounds are usually transient and may be misinterpreted or missed altogether.[23] The precordial Doppler and transesophageal echocardiogram may detect small amounts of air even before physiologic changes are evident.[29] A decrease in end-tidal CO_2, an increase in pulmonary artery pressure, and a decrease in arterial O_2 saturation require progressively larger amounts of air than that detected by precordial Doppler and transesophageal echocardiogram.[25] Other objective signs such as dyspnea, circulatory insufficiency, and pulmonary hypertension, although nonspecific, may aid in the diagnosis of venous air embolism.

Relatively specific signs of CAGE are air in the retinal vessels and, more uncommonly, sharply defined areas of pallor on the tongue (Liebermaster's sign) and marbling of the skin.[30] Additionally, subcutaneous air, mediastinal emphysema, or pneumothorax may be seen.[31] The diagnosis of CAGE becomes firmer when there are multiple neurologic findings that cannot be explained by compromised blood flow from a single anatomic area. The multifocality of manifestations results from the emboli not being confined to a single arterial supply.[15] Other more subtle diagnostic manifestations may include abnormalities in neuropsychological batteries for apraxia, agnosia, right-to-left disorientation, speech and fluency, reading, and memory.[32]

While computerized tomographic scanning, magnetic resonance imaging, single photon-emission computed tomography, or stable xenon-enhanced computerized tomographic scanning of the head may aid in the diagnosis of CAGE, our experience[33] is that these studies are frequently inconclusive and may delay the initiation of therapy; thus, we do not routinely recommend them. However, while the diagnosis of CAGE is being considered, and certainly once it has been made, continuous electrocardiographic monitoring is recommended because cardiac arrest,[31] ischemia, and dysrhythmias may occur.[16]

Pathophysiology

The pathophysiology of CAGE and the extent of the damage that results depend on the amount of air involved and the length of time after embolization until therapy (for example, hyperbaric O_2 therapy) is initiated.[34] Whereas the clinical syndrome depends on the point of entry and the destination of the air,[14] controversy exists as to the principal factor(s) responsible for tissue damage following CAGE. Cerebral arterial gas embolism causes injury to the central nervous system by obstructing flow and provoking ischemia. Although location, duration, and the extent of ischemia are thought by many to be important, post-ischemic events may be equally, if not more, important.[35]

In a dog model, de la Torre and colleagues[36] found that CAGE produced acute focal zones of "blanching" of white matter with perivascular swelling, on microscopic examination. In those animals that died less than 48 hours after embolism, macroscopic examination showed dilation of vasculature, swollen brain, and herniation of the piriform and cingulate gyri. In those dogs surviving to 1 week after embolism, microscopic examination of infarcted areas showed liquefactive necrosis, vascular hyperplasia, neuronal degeneration, and the presence of phagocytes. The etiology of the infarctions was ischemic rather than hemorrhagic. The

group also found an immediate rise in cisternal pressure after embolization, which correlated with morbidity and mortality.[36]

Evans et al[37] reported that in ventilated, anesthetized cats, embolization of the vertebral artery with 2 mL/kg of air resulted in acute arterial hypertension, increased heart rate, increased left ventricular pressure and contractility, and severe cardiac dysrhythmias. If the autonomic nervous system response was blocked via surgical or pharmacologic denervation, only the dysrhythmias were prevented; neither the acute hypertensive response, the elevated heart rate, nor the augmented contractility resulting from CAGE was attenuated. The authors postulated that an unidentified humoral substance was released from the cerebral circulation that was responsible for the cardiovascular responses.

Babcock and Netsky[15] showed that internal carotid artery injection of 0.6 to 0.8 mL of barium sulfate and celloidin into dogs produced apnea, whereas smaller volumes resulted in Cheyne-Stokes respirations or a slowed respiratory pattern. The alteration in respiratory pattern appeared to be related to the total volume of cerebral tissue that was rendered ischemic and not to damage in any one particular area of the brain. They theorized that cerebral arterial embolization resulted in damage to the brainstem respiratory centers.

In a study involving 97 dogs, Leitch and colleagues[38] found, after injection of 0.4 mL of air into the right internal carotid artery, an immediate decrease in cerebrospinal fluid pressure often followed by an increase of up to 20 mm Hg. Amplitude of somatosensory-evoked potentials (SEPs) 1 minute after embolization was decreased by 30 to 100% of baseline. Return of cortical-evoked potentials depended primarily on the degree of initial suppression and the time to definitive therapy (recompression).

Air usually lodges in arteries of 30-60 μ in diameter.[39] Use of ^{99m}Tc-labelled hexamethylpropylineamine oxime and single photon-emission tomography allows practical imaging of cerebral perfusion deficits. The pattern of isotope uptake with CAGE suggested that perfusion deficits are caused by heterogenous small vessel blockage rather than by occlusion of larger vessels.[35] Additionally, secondary effects of intravascular bubbles have been reported. Air embolization causes dilation of vessels in tissue surrounding the ischemic areas; these vessels no longer exhibit autoregulation of flow to changes in blood pressure.[39] Intravascular air bubbles cause activation of platelets and leukocytes, and the formation of microthrombi, which may play a role in the extension of ischemic damage. Vasoactive substances (such as serotonin, kinins, and prostaglandins) are also released. Hemoconcentration often occurs, which may further impair cerebral flow secondary to increased viscosity.[39]

Lee and Olszewski[40] reported an increase in cerebral vascular permeability to heterologous albumin in cats after injection of 0.1 to 0.4 mL of air into the common carotid artery. This permeability was transient, lasting approximately 1 hour after the CAGE incident. Fritz and Hossmann showed that the cerebral acidosis present after the embolic event was associated with vasoparalysis.[35] There was inhomogeneity of blood flow with tissue ischemia at the embolism site and hyperemia of surrounding tissues. Unlike Lee and Olszewski,[40] Fritz and Hossman[35] did not find disruption of the blood-brain barrier. Thus, although there was an increase in brain volume, there was no significant increase in brain water. Other findings within 15 seconds after embolism included loss of electroencephalographic amplitude and frequency to approximately 30% of baseline with gradual recovery after 1 hour. Depression of the electroencephalogram was related to duration of ischemia and was slowest to return in the border zones, where perfusion pressure was lowest. Uncoupling of blood flow and metabolism occurred (blood flow increased and metabolism decreased), resulting in elevated cerebral venous oxygen content. In contrast, Levy and Duffy[41] reported that cerebral ischemia in gerbils produced a marked depletion of high energy phosphate reserves. Their assumption was that abnormal energy metabolism and oxygen consumption in post-ischemic tissue may contribute to worsening neurologic function and irreversible damage.

An unfortunate problem with these data is that the studies were primarily carried out in animal models. It is not intuitive which animal model/species is most appropriate for the study of CAGE or how the findings in one species relates to another. Finally, the extent to which these data can be extrapolated to humans is unclear.

Issues in the Treatment of CAGE

Standard recompression therapy with adjunctive drugs and fluids results in about 85% recovery, even after delays of many hours. However, 15% of patients will suffer permanent deficits or death.[42]

Immediate Treatment

Once the diagnosis of air embolization is suspected, the patient should be placed in the 30° head-down position. The left lateral decubitus position (Durant's maneuver) allows air bubbles in the right ventricular outflow tract to move toward the apex of the heart, thus enhancing forward flow of blood.[43] This position may help avoid pulmonary aspiration of gastric contents should emesis occur in the unconscious victim; while it may help prevent further embolization, it does nothing for material already in circulation. Because diffusion of nitrogen out of air bubbles will be maximized by inhalation of 100% O_2,[14] it should be administered via a tight-fitting mask while the patient is en route to the recompression chamber.[42] The increased arterial oxygen tension serves to deliver a slightly increased amount of oxygen to the affected tissues,[16] but is primarily used to maximize the nitrogen gradient, although it has also been shown in other scenarios to constrict cerebral blood vessels, reduce cerebral blood flow,[44] and decrease intracranial pressure (ICP).

If intravenous fluids are necessary, isotonic ones (such as 0.9% saline) should be administered to maintain the urine output at approximately 0.5 mL/kg/h and to prevent hemoconcentration with resultant decreased oxygen delivery. While there are no data evaluating the effects of hypertonic saline resuscitation in victims of CAGE, animal studies have suggested that hypertonic saline helps prevent elevation of ICP following the injury. Some,[45,46] but not all,[47,48] studies that have attempted to evaluate the differential effect of hypertonic versus isotonic or hypotonic fluid to resuscitate from hemorrhage[45,47,48] or hemodilution[46] without brain injury, have noted that ICP was lower in the experimental subjects (rabbits, dogs, and pigs) in which hypertonic solutions were used. In one study, in which animals suffered a focal cryogenic brain injury,[49] cerebral blood flow (CBF) was higher and ICP lower in animals infused with hypertonic sodium lactate (500 mOsm/L) as compared to lactated Ringer's solution (270 mOsm/L). We reiterate that these studies were not performed in a model of CAGE and, thus, must be interpreted cautiously. Studies to evaluate the effects of different resuscitation solutions in a model of CAGE and Type II DCS are eagerly awaited.

Two animal studies—again not in a model of CAGE—evaluated outcome in complete[50] or incomplete[51] cerebral ischemia. These results suggest that fluid replacement with solutions containing glucose result in significantly worse neurologic outcome than does replacement with a crystalloid without glucose. Finally, a recent human study suggests that elevated blood glucose levels and reduced cerebral blood flow measured by the stable xenon technique correlate with poor outcome.[52] Thus, we use no solution containing glucose for emergency resuscitation unless the measured blood glucose is subnormal.

In-Transit Treatment

While in transit, patients suspected of having suffered a CAGE or Type II DCS should have (in addition to standard vital signs) pulse oximetry and electrocardiographic monitoring and frequent neurologic system checks. Fluids are used as detailed above. Our preference is to use 0.9% or 3% saline solutions at three fourths the maintenance rate unless urine output is < 0.5 mL/kg/h. Maintenance rate is calculated using the "4/2/1" rule: 4 mL/kg/h for the first 10 kg, 2 mL/kg/h for the second 10 kg, and 1 mL/kg/h for every kg thereafter. Thus, for a 70-kg person, the full maintenance rate would be 40 mL + 20 mL + 50 mL = 110 mL/h. We would administer about three fourths of this (80 mL) hourly. Note that if 3% saline solution is used, the full maintenance rate is only one third as much as calculated for 0.9% saline solution (about 35 mL/h). In this case we would administer three fourths of that rate, or about 25 mL/h. Again, as noted above, no glucose containing solutions are used in the absence of hypoglycemia.

In-Hospital Treatment

Fluid therapy and monitoring are continued as described above. Moreover, tight serum-glucose

control, in the range of 80 to 150 mg/dL, (4.4-8.3 mmol/L) is maintained through judicious insulin use based on the data cited above regarding outcome in cerebral ischemia. Compression to 6 atm will theoretically reduce the size of an air bubble to one sixth its original volume, in compliance with Boyle's Law.[2] Immediate recompression mechanically decreases the size of the embolus and permits peripheral relocation or reabsorption of the embolus.[53] However, delayed compression therapy, even 10 to 14 days after the injury, has been reported to be beneficial for residual bubble effects and distal tissue hypoxia.[54]

In the past, use of the U.S. Navy recompression Tables 5, 6, and 6A,[42] adapted for Figure 1, has generally been accepted for the treatment of CAGE. Bond et al[55] recently reported that there was no significant improvement in the outcome of divers with CAGE treated with Navy Table 6 versus 6A (Fig. 1B and Fig. 1C). This is of some significance because the former requires compression to only 60 feet seawater and the latter to 120 feet. McDermott et al[56] measured recovery of somatosensory-evoked potentials in anesthetized, ventilated cats randomized to three treatment protocols. Air was infused into the carotid artery until the cortical SEP amplitude was reduced to less than 10% of baseline. The control group received no further treatment after SEP suppression. A second group was compressed to 6 atm (approximately 120 feet seawater) in air for 30 minutes, then given 100% oxygen at 2.8 atm (approximately 60 feet seawater) for 100 minutes. The third group was compressed to 2.8 atm on 100% oxygen for 130 minutes. The two treatment groups could not be distinguished from each other statistically based on recovery of SEP amplitude. McDermott et al[56] postulate that treating CAGE at 2.8 atm with 100% oxygen may be an alternative to the current compression to 6 atm on air prior to hyperbaric oxygen therapy for CAGE. Monoplace chambers can compress to 60 feet but not 120 feet and are generally easier to locate than are multiplace chambers with greater depth capability. McDermott et al suggest that further studies be performed to determine the usefulness of increasing concentrations of oxygen at 6 atm during initial recompression for CAGE. A recent editorial, however, warns against attempting to associate SEP recovery with improved neurologic outcome.[57] The magnitude and duration of cortical SEP amplitude alterations may be important predictors of outcome. Also important is whether the electrophysiologic variables revert to normal.

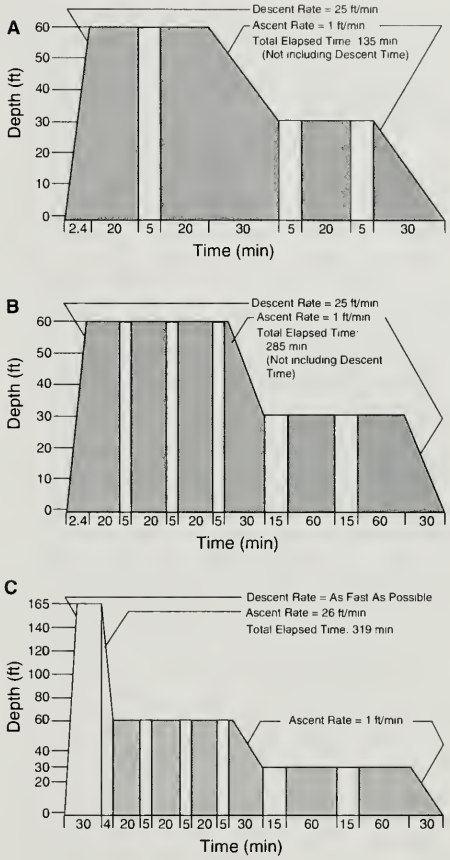


Fig. 1. Navy recompression Table 5 (A), 6 (B), and 6A (C).[42] The dark areas of the figure are time periods during which the F_{IO_2} is 1.0; the light areas are air breathing periods. The X-axis gives the time frame for each of the activities, whereas the Y-axis shows the depth at which they occur.

Even though the side effects of recompression therapy are generally minimal, oxygen is toxic when used for prolonged periods of time or at high ambient pressures. Symptoms of pulmonary oxygen-toxicity include irritation and decreased com-

pliance and convulsions (at pressures greater than 3 atm).[13] Our experience is that a sensation of burning with deep inspiration is relatively common in patients treated repetitively in the hyperbaric chamber. Resolution usually requires nothing more than delay of further compression for several days. At our center, presumed CAGE is still treated using Navy Table 6A (Fig. 1C); however, we are re-evaluating our practice based on the above-cited animal work.

Many adjuvant drug therapies have been proposed for CAGE.[39] Intravenous steroids are used for maintenance of capillary endothelial integrity,[42,58] but several hours must pass before their effect is apparent. Pearson and Goad[59] noted a significant reduction in the incidence of relapse following the introduction of high-dose steroid regimens and asserted that relapse is secondary to cerebral edema from disruption of the blood-brain barrier. However, other studies have failed to demonstrate this disruption or vasogenic edema.[35] Diuretics in combination with steroids may be helpful for treatment of cerebral edema, but experience has been limited.[39]

Anticoagulants (such as heparin, which might be helpful in the resolution of thrombi) are relatively contraindicated in air embolization secondary to the risk of hemorrhage; aspirin may be of some use but is, at present, controversial. Animal experiments have shown that naloxone administration resulted in improved neuronal function after stroke; however, no controlled studies exist in humans to substantiate its use following CAGE. Reduction of ICP using lidocaine was studied by Evans and Kobrine[60] in anesthetized, ventilated cats. Their model involved infusion of 1 mL/kg air at a rate of 2 mL/min into the vertebral artery. The mean (±SD) ICP rose from 11 (3) mm Hg at baseline to 69 (10) mm Hg 3 to 4 minutes after the air infusion. Intracranial pressure in animals pretreated with 5 mg/kg lidocaine increased from 12 (1) mm Hg to only 23 (5) mm Hg 3 to 4 minutes after embolization. The authors postulate that intravenous lidocaine caused vasoconstriction of cerebral vessels and thus a decrease in cerebral blood flow. Another possible mechanism depends upon the fact that lidocaine acts at the Na^+–K^+ channel. Increased extracellular K^+ may occur secondary to abnormal function of transport mechanisms, causing neuronal depolarization with subsequent movement of calcium into the cells,[39] possibly causing cell death. Lidocaine may help prevent the accumulation of this extracellular K^+. Further, the antiarrhythmic effects of this agent may help preserve cardiac output and cerebral perfusion pressure, and, at appropriate blood levels, lidocaine's general anesthetic effects may prevent increased oxygen consumption secondary to seizure activity. However, the effect of lidocaine in various ischemic models has yielded conflicting results. For instance, in one study, McDermott et al[61] were unable to demonstrate a significant benefit from adding lidocaine to recompression therapy in a cat model of cerebral air embolism. Yet, in another investigation, this same group found that lidocaine added benefit to hyperbaric oxygen therapy in a canine model of cerebral air embolism.[62] Differences in animal species and treatment protocol, other than the utilization of lidocaine, may partly explain these differences. Finally, no controlled studies in humans exist to validate the routine use of lidocaine in patients with CAGE. Other adjunctive therapies such as calcium-channel blockers and oxygen free-radical scavengers have been used, but further demonstration of their efficacy is required.[39]

In Summary

CAGE is a disease that is reasonably difficult to diagnose with certainty, and its therapy has not undergone rigorous controlled study in humans. Although several excellent animal studies have been performed, definitive research on this pathologic entity has yet to be designed and conducted.

ACKNOWLEDGMENTS

We appreciate the editorial help of Suzanne White and the critical review given by our colleagues T James Gallagher MD and Michael Mahla MD.

REFERENCES

1. Brenner WI. A battle plan in the event of massive air embolism during open heart surgery. J Extra-Corporeal Technol 1985;17:133-137.
2. Murphy BP, Harford FJ, Cramer FS. Cerebral air embolism resulting from invasive medical procedures: treatment with hyperbaric oxygen. Ann Surg 1985; 201(2):242-245.
3. Gronert GA, Messick JM Jr, Cucchiara RF, Michenfelder JD. Paradoxical air embolism from a patent foramen ovale. Anesthesiology 1979;50(6):548-549.

4. Fong J, Gadalla F, Druzin M. Venous emboli occurring during caesarean section: the effect of patient position. Can J Anaesth 1991;38(2):191-195.
5. Omenaas E, Moerkve O, Thomassen L, Daehlin L, Larsen J, Eidsvik S, et al. Cerebral air embolism after transthoracic aspiration with a 0.6 mm (23 gauge) needle. Eur Respir J 1989;2(9):908-910.
6. Cianci P, Posin JP, Shimshak RR, Singzon J. Air embolism complicating percutaneous thin needle biopsy of lung. Chest 1987;92(4):749-751.
7. Naulty JS, Meisel LB, Datta S, Ostheimer GW. Air embolism during radical hysterectomy. Anesthesiology 1982;57(5):420-422.
8. Kindwall EP, Nemiroff MJ. Pulmonary overpressure accidents. In: Behnke AR, ed. Hyperbaric and undersea medicine. San Antonio: Medical Seminars, 1981:3-6.
9. Aronson ME, Nelson PK. Fatal air embolism in pregnancy resulting from an unusual sexual act. Obstet Gynecol 1967;30(1):127-130.
10. Fyke FE 3rd, Kazmier FJ, Harms RW. Venous air embolism: life-threatening complication of orogenital sex during pregnancy. Am J Med 1985;78(2):333-336.
11. Adkisson GH, Macleod MA, Hodgson M, Sykes JJW, Smith F, Strack C, et al. Cerebral perfusion deficits in dysbaric illness. Lancet 1989;2(8655):119-122.
12. Lamphier E. Management of sports diving accidents. NY State J Med 1963;63:667.
13. Greer HD, Massey EW. Neurologic injury from undersea diving. Neurol Clin 1992;10(4):1031-1045.
14. Francis TJR, Pearson RR, Robertson AG, Hodgson M, Dutka AJ, Flynn ET. Central nervous system decompression sickness: latency of 1070 human cases. Undersea Biomed Res 1988;15(6):403-417.
15. Babcock RH, Netsky MG. Respiratory and cardiovascular responses to experimental cerebral emboli. Arch Neurol 1960;2:556-564.
16. Gorman DF. Decompression sickness and arterial gas embolism in sports scuba divers. Sports Med 1989;8(1): 32-42.
17. Calder IM, Palmer AC, Hughes JT, Bolt IF, Buchanan JD. Spinal cord degeneration associated with Type II decompression sickness: case report. Paraplegia 1989;27 (1):51-57.
18. Marini JJ, Culver BH. Systemic gas embolism complicating mechanical ventilation in the adult respiratory distress syndrome. Ann Intern Med 1989;110(9):699-703.
19. Morris WP, Butler BD, Tonnesen AS, Allen SJ. Continuous venous air embolism in patients receiving positive end-expiratory pressure. Am Rev Respir Dis 1993; 147(4):1034-1037.
20. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;59(1):17-20.
21. Black S, Cucchiara RF, Nishimura RA, Michenfelder JD. Parameters affecting occurrence of paradoxical air embolism. Anesthesiology 1989;71(2):235-241.
22. Butler BD, Hills BA. Transpulmonary passage of venous air emboli. J Appl Physiol 1985;59(2):543-547.
23. Dick APK, Massey EW. Neurologic presentation of decompression sickness and air embolism in sport divers. Neurology 1985;35(5):667-671.
24. Gorman DF. Arterial gas embolism as a consequence of pulmonary barotrauma. In: Diving and hyperbaric medicine IX. Barcelona: European Undersea Biomedical Society, 1984:348-368.
25. Baskin SE, Wozniak RF. Hyperbaric oxygenation in the treatment of hemodialysis-associated air embolism. N Engl J Med 1975;293(4):184-185.
26. Stonier JC. A study in prechamber treatment of cerebral air embolism patients by a first provider at Santa Catalina Island (abstract). Undersea Biomed Res 1985; 12(Suppl):58.
27. Kizer KW. Dysbaric cerebral air embolism in Hawaii. Ann Emerg Med 1987;16(5):535-541.
28. Hoffman EP, Fiskin RD, Shelden CH. Unusual heart sounds associated with venous air embolism: case report. J Neurosurg 1970;33(4):460-462.
29. Ostman PL, Pantle-Fisher FH, Faure EA, Glosten B. Circulatory collapse during laparoscopy. J Clin Anesth 1990;2(2):129-132.
30. Armon C, Deschamps C, Adkinson C, Fealey RD, Orszulak TA. Hyperbaric treatment of cerebral air embolism sustained during an open-heart surgical procedure. Mayo Clin Proc 1991;66(6):565-571.
31. Bayne CG, Wurzbacher T. Can pulmonary barotrauma cause cerebral air embolism in a non-diver? Chest 1982;81(5):648-650.
32. Neuman TS, Hallenbeck JM. Barotraumatic cerebral air embolism and the mental status examination: a report of four cases. Ann Emerg Med 1987;16(2):220-223.
33. Layon AJ. Hyperbaric oxygen treatment for cerebral air embolism—where are the data? (editorial). Mayo Clin Proc 1991;66(6):641-646.
34. Winter PM, Alvis HJ, Gage AA. Hyperbaric treatment of cerebral air embolism during cardiopulmonary bypass. JAMA 1971;215(11):1786-1788.
35. Fritz H, Hossmann K-A. Arterial air embolism in the cat brain. Stroke 1979;10(5):581-589.
36. de la Torre E, Meredith J, Netsky MG. Cerebral air embolism in the dog. Arch Neurol 1962;6:307-316.
37. Evans DE, Kobrine AI, Weathersby PK, Bradley ME. Cardiovascular effects of cerebral air embolism. Stroke 1981;12(3):338-344.
38. Leitch DR, Greenbaum LJ Jr, Hallenbeck JM. Cerebral arterial air embolism—II. effect of pressure and time on cortical evoked potential recovery. Undersea Biomed Res 1984;11(3):237-248.
39. Dutka AJ. A review of the pathophysiology and potential application of experimental therapies for cerebral ischemia to the treatment of cerebral arterial gas embolism. Undersea Biomed Res 1985;12(4):403-421.
40. Lee JC, Olszewski J. Effect of air embolism on permeability of cerebral blood vessels. Neurology 1959;9:619-625.
41. Levy DE, Duffy TE. Cerebral energy metabolism during transient ischemia and recovery in the gerbil. J Neurochem 1977;28(1):63-70.

42. Davis JC, Youngblood DA. Definitive treatment of decompression sickness and arterial gas embolism. In: Behnke AR, ed. Hyperbaric and undersea medicine. San Antonio: Medical Seminars, 1981:2-7.
43. Alvaran SB, Toung JK, Graff TE, Benson DW. Venous air embolism: comparative merits of external cardiac massage, intracardiac aspiration, and left lateral decubitus position. Anesth Analg 1978;57(2):166-170.
44. Nakajima S, Meyer JS, Amano T, Shaw T, Okabe T, Mortel KF. Cerebral vasomotor responsiveness during 100% oxygen inhalation in cerebral ischemia. Arch Neurol 1983;40(5):271-276.
45. Prough DS, Johnson JC, Poole GV Jr, Stullken EH, Johnston WE Jr, Royster R. Effects on intracranial pressure of resuscitation from hemorrhagic shock with hypertonic saline versus lactated Ringer's solution. Crit Care Med 1985;13(5):407-411.
46. Todd MM, Tommasino C, Moore S. Cerebral effects of isovolemic hemodilution with a hypertonic saline solution. J Neurosurg 1985;63(6):944-948.
47. Ducey JP, Lamiell JM, Gueller GE. Cerebral electrophysiologic effects of resuscitation with hypertonic saline-dextran after hemorrhage. Crit Care Med 1990;18(7):744-749.
48. Prough DS, Whitley JM, Olympio MA, Taylor CL, DeWitt DS. Hypertonic/hyperoncotic fluid resuscitation after hemorrhagic shock in dogs. Anesth Analg 1991;73(6):738-744.
49. Shackford SR, Zhuang J, Schmoker J. Intravenous fluid tonicity: effect on intracranial pressure, cerebral blood flow, and cerebral oxygen delivery in focal brain injury. J Neurosurg 1992;76(1):91-98.
50. Lanier WL, Stangland KJ, Scheithauer BW, Milde JH, Michenfelder JD. The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: examination of a model. Anesthesiology 1987;66(1):39-48.
51. Hoffman WE, Braucher E, Pelligrino DA, Thomas C, Albrecht RF, Miletich DJ. Brain lactate and neurologic outcome following incomplete ischemia in fasted, non-fasted, and glucose-loaded rats. Anesthesiology 1990; 72(6):1045-1050.
52. Ashwal S, Schneider S, Tomasi L, Thompson J. Prognostic implications of hyperglycemia and reduced cerebral blood flow in childhood near-drowning. Neurology 1990;40(5):820-823.
53. Gillen HW. Symptomatology of cerebral gas embolism. Neurology 1968;18(5):507-512.
54. Myers RAM, Bray P. Delayed treatment of serious decompression sickness. Ann Emerg Med 1985;14(3):254-257.
55. Bond JG, Moon RE, Morris DL. Initial table treatment of decompression sickness and arterial gas embolism. Aviat Space Environ Med 1990;61(8):738-743.
56. McDermott JJ, Dutka AJ, Koller WA, Pearson RR, Flynn ET. Comparison of two recompression profiles in treating experimental cerebral air embolism. Undersea Biomed Res 1992;19(3):171-185.
57. Warner DS. Editorial comment [on: Dutka AJ, Mink R, McDermott J, Clark JB, Hallenbeck JM. Effect of lidocaine on somatosensory evoked response and cerebral blood flow after canine cerebral air embolism. Stroke 1992;23(10):1515-1520]. Stroke 1992;23(10):1520-1521.
58. Bove AA, Clark JM, Simon AJ, Larnbertsen CJ. Successful therapy of cerebral air embolism with hyperbaric oxygen at 2.8 ATA. Undersea Biomed Res 1982; 9(1):75-80.
59. Pearson RR, Goad RF. Delayed cerebral edema complicating cerebral arterial gas embolism: case histories. Undersea Biomed Res 1982;9(4):283-296.
60. Evans DE, Kobrine AI. Reduction of experimental intracranial hypertension by lidocaine. Neurosurgery 1987;20(4):542-547.
61. McDermott JJ, Dutka AJ, Evans DE, Flynn ET. Treatment of experimental cerebral air embolism with lidocaine and hyperbaric oxygen. Undersea Biomed Res 1990;17(6):525-534.
62. Dutka AJ, Mink R, McDermott J, Clark JB, Hallenbeck JM. Effect of lidocaine on somatosensory evoked response and cerebral blood flow after canine cerebral air embolism. Stroke 1992;23(10):1515-1520.

AARC
American Association for Respiratory Care
40th Annual Convention and Exhibition
December 10-13, 1994 • Las Vegas, Nevada

Share RC Information & Help Your Community Breathe Easier

Requirements For Traveling With Oxygen

Oxygen patients who travel need to know the requirements for the various carriers they use. This handy eight-page booklet contains phone numbers and basic requirements for airlines, cruise lines, the Greyhound bus system, and AMTRAK.

BK16

$20, Pkg 50

(AARC Member $10)

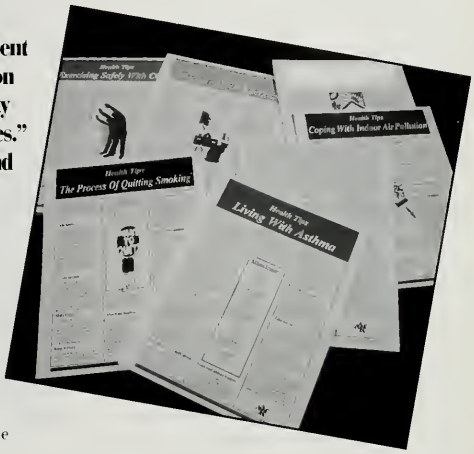
To Order Call (214) 243-2272

FAX Your Order To (214) 484-2720 or (214) 484-6010

Use these health tips sheets as a community relations tool or for patient education. Sharing this information with your patients and community shows that "Respiratory Care…Cares." Comes 50 to a pad. Convenient and easy to tear off.

$10 Ea, Pad 50

(AARC Member $5)



Helping Your Child Breathe Easier
More tips from the AARC for helping alleviate respiratory problems in children. Presents pointers on colds, flu, allergies, and other childhood respiratory illnesses. **Item R23**

Secondhand Smoke
This brochure offers topical information about the effects of exposure to secondhand smoke and how to avoid it in public, at the office, and in the home. **Item R24**

Eating Right: Tips for the COPD Patient
Patients with lung disease must be more careful than most about following good nutrition. Includes tips on what to eat and avoid and the best times for eating. **Item R25**

Dealing with Allergies
More than 35 million Americans suffer from allergies, and this sheet gives them pointers on reducing or avoiding exposure to allergens, preventing respiratory infection, and using medications as instructed. **Item R30**

Minimizing the Effects of Outdoor Air Pollution
Everyone is adversely affected by air pollution. This tip sheet discusses avoidance of exposure to noxious fumes and the importance of staying updated on pollution reports. **Item R31**

Living with Asthma
Ten million U.S. citizens have asthma, and this tip sheet gives them pointers on following their doctor's advice. Also helps them understand medications, avoid triggers, and maintain good health. **Item R32**

The Process of Quitting Smoking
Every year, three million smokers give up cigarettes. You can help others quit with these tips on how they can start the process. **Item R33**

Coping with Indoor Air Pollution
Indoor air pollution affects everyone. This tip sheet gives pointers on coping with 13 types of indoor air pollution from tobacco smoke to radon gas. **Item R34**

Exercising Safely with COPD
COPD patients need exercise, too, and this tip sheet gives advice on doing it safely from warm-up to cool-down. **Item R35**

Lessening the Effects of COPD
Much can be done to lessen the side effects and symptoms of COPD. This sheet gives advice on how these patients can lead an active and rewarding life. **Item R36**

Hypoxemia in a Postpartum Patient with Complex Congenital Heart Disease

Henry Vega MD and Charles G Durbin Jr MD

A 25-year-old woman with Eisenmenger's syndrome (ES) was admitted at 34-weeks gestation for elective cesarean-section delivery and surgical sterilization. She had been born with transposition of the great vessels and a ventricular septal defect (VSD) and underwent a Mustard procedure at age 13 years. Since then she had had good exercise tolerance. At 18-weeks gestation, she began to experience shortness of breath with moderate exertion and at 20-weeks gestation she developed supraventricular tachycardia and worsening shortness of breath. She was treated with digoxin and her heart converted to sinus rhythm. At that time, her P_{aO_2} on room air was 52 torr. She was started on continuous oxygen at 2 L/min, resulting in improvement of her hypoxemia, and she continued to use oxygen for the remainder of her pregnancy.

Dr Vega is Staff Anesthesiologist, Moorehead Memorial Hospital, Eden, North Carolina, and Dr Durbin is Professor of Anesthesiology and Surgery, University of Virginia Health Sciences Center, Charlottesville, Virginia.

After placement of catheters for monitoring central venous pressure (CVP) and for arterial sampling, the patient underwent an uneventful low-transverse cesarean-section delivery under epidural anesthesia. She was transferred to the surgical intensive care unit (SICU) for postoperative care and monitoring. On admission to the SICU, the patient was given oxygen by nonrebreathing mask, and her hemoglobin saturation, measured by pulse oximetry, ranged 98-100%. By the third postoperative day she had been weaned to oxygen by nasal cannula at 2 L/min and was maintaining normal arterial saturation. Subcutaneous sodium heparin was begun at that time to reduce the risk of thrombosis.

Later that day, her oxygen saturations were noted to be decreased (range of 84-89%), despite the increase in F_{IO_2} that resulted from oxygen administration using a nonrebreathing face mask. Her measured CVP was 6-8 mm Hg at that time and fluids were given to treat presumed right-to-left shunting from decreased pulmonary blood flow. Her CVP did not change despite the administration of more than 2 L of fluid. Hypoxemia persisted, and a chest radiograph was taken (Fig. 1).

How would you answer these questions?

What does the chest radiograph show? _____

_____

_____

_____

Fig. 1. Anteroposterior chest radiograph of a 25-year-old woman 3 days after she underwent an elective cesarean-section delivery and surgical sterilization.

What is the likely cause of hypoxemia in this patient? _____

_____

_____

_____

What is the pathophysiologic basis of hypoxemia in Eisenmenger's syndrome? _____

_____

_____

_____

What therapeutic options exist for this patient? _____

_____

_____

_____

Answers and Discussion on Next Page

Answers

Chest Radiograph Findings: The chest radiograph shows a right upper lobe (RUL) density with rightward deviation of the upper trachea and other mediastinal structures. An enlarged cardiac shadow can be seen, with left ventricular prominence and blunting of the right costophrenic angle (small pleural effusion). The evidence of the previous sternotomy for Mustard repair of transposition of the great vessels—five sternal wires—is also apparent, and the central line, seen outside the thorax, is kinked back upon itself.

Cause of Hypoxemia: The radiograph shows RUL collapse. In RUL collapse, the apical segment usually collapses toward the mediastinum. The radiopacity of the RUL depends on the degree of collapse, making the diagnosis of partial collapse difficult from the anteroposterior view. Classic signs of RUL collapse include elevation of the minor fissure (seen as the lower edge of the RUL shadow in Fig. 1), fuzzy right-lateral border of the superior mediastinum, and loss of definition of the upper-right margin of the ascending aorta. Tracheal deviation toward the right is not often seen but, in this case, was easy to recognize. RUL collapse with resultant intrapulmonary—not intracardiac—shunting of blood was the cause of this patient's hypoxemia.

Pathophysiologic Basis of Hypoxemia: The radiographic findings in ES seen in this patient included cardiomegaly, a small right-side pleural effusion (indicative of cardiac failure), and large pulmonary arteries indicating pulmonary hypertension. These classic radiographic signs of Eisenmenger's are illustrated in Figure 2. The radiologic criterion for the diagnosis of pulmonary hypertension in this patient is the increased diameter of the right inferior pulmonary artery.

The pathophysiology of ES is that chronic pulmonary hypertension leads to reversal of the usual left-to-right intracardiac shunt and produces bidirectional or right-to-left shunt, causing profound arterial desaturation. Any condition that alters the delicate balance between the right and left circulations may make the shunt worse and cause hypoxemia. A low cardiac output due either to inadequate cardiac filling pressures or a rise in pulmonary pressures is often a cause of hypoxemia in patients with ES.

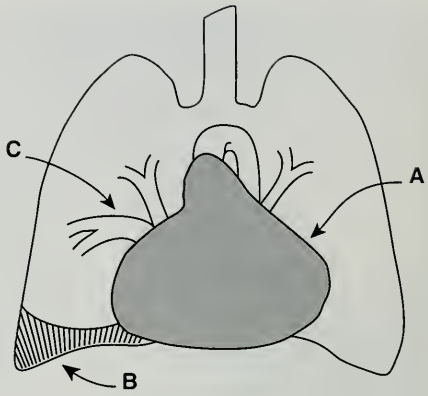


Fig. 2. The radiologic signs of Eisenmenger's syndrome are illustrated in this drawing. (A) cardiomegaly (cardiothoracic ratio > 0.5), (B) congestive heart failure causing pleural effusion, and (C) large inferior pulmonary artery (diameter > 1 cm).

We assumed that, in this case, the low postoperative values of CVP indicated hypovolemia. The fluid administration was our attempt to decrease the presumed right-to-left intracardiac shunt. From the radiograph taken after the patient failed to improve (Fig. 1), the accuracy of the CVP measurement was challenged because the catheter appeared to be malpositioned, which meant that the measurement of CVP was not a true indication of intravascular volume.

Therapeutic Options: The therapeutic options available to reverse lobar collapse include aggressive chest physiotherapy,[1] incentive spirometry, and endotracheal suctioning.[2] Occasionally bronchoscopy is necessary to remove a mucus plug. In mechanically ventilated patients, it's often helpful to increase the tidal volume and PEEP levels. This patient never became dyspneic postoperatively and was successfully treated with chest physiotherapy and upright positioning. The chest radiograph shown in Figure 3 shows resolution of the RUL collapse with return of the trachea to midline, but the small right pleural effusion (medial-costophrenic-angle blunting) persists. The central line has been removed.

Fig. 3. Anteroposterior chest radiograph was taken after 2 days of chest physiotherapy and upright positioning and shows full resolution of the RUL atelectasis. The small medial-costophrenic pleural effusion persists.

Discussion

Options for palliative surgical correction for a patient with transposition of the great vessels (TGV) include the Rashkind-Miller balloon atrial septostomy and the Blalock-Hanlon open atrial septectomy. The principle behind these two procedures is to establish (or increase) an anatomical connection between the right and left sides of the heart that allows mixing of deoxygenated blood with oxygenated blood. This promotes both patient survival and growth. At a later stage, a more definitive procedure can be considered.

Definitive repairs of TGV can be made at the atrial or ventricular level. In the Mustard procedure pericardial or prosthetic material and in the Senning procedure the atrial wall itself are used to separate and redirect blood to the transposed ventricles. Atrial and ventricular septal defects are closed to completely separate the pulmonary and systemic circulations. Unfortunately, the anatomically 'incorrect' ventricle (right ventricle) cannot assume the pressure-load meant for the left ventricle indefinitely, and patients who undergo these procedures usually die in their mid-to-late twenties of heart failure.

Arterial-switch operations—Jatene, Norwood, and Damus-Kaye-Stansel procedures—result in the 'correct' ventricle pumping blood to the 'correct' circuit.[3] The right ventricle pumps to the pulmonary circulation and the left ventricle pumps to the systemic circulation. In theory, patients who have these procedures should live longer; however, operative mortality is higher in patients who undergo definitive repair. Because these procedures are relatively new, effects on longevity are not known for certain.

In this patient, although a Mustard procedure had been performed, the VSD was left open because pulmonary hypertension was already present. The persistently increased pulmonary blood flow that resulted, produced further increases in PVR and, finally, Eisenmenger's syndrome.

Eisenmenger's syndrome occurs when pulmonary hypertension develops and causes bidirec-

tional or right-to-left shunting of blood through an intracardiac or intrapulmonary communication.[1] It can occur secondary to complex congenital malformations, various septal defects, or patent ductus arteriosus. VSD is the septal defect that is most commonly associated with ES. The two events that cause most of the problems seen in pregnant patients with ES are (1) a decrease in the systemic blood pressure leading to increased right-to-left shunt and hypoxemia, and (2) thromboembolic events leading to further pulmonary embarrassment or paradoxic cerebral emboli (emboli that arise from the systemic circulation, pass through the VSD, and lodge in a cerebral artery).[4]

The pathophysiologic basis for the acute changes seen in ES involve the tenuous balance between the systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR). Any change that produces a decrease in SVR or an increase in PVR serves to augment the degree of right-to-left shunt, which worsens hypoxemia and further increases PVR.

Patients with ES often have the associated physical findings of chronic hypoxemia, including cyanosis, digital clubbing, and elevated hematocrit. Exertional dyspnea and fatigue are common, and heart failure, arrhythmias, syncope, chest pain, hemoptysis, and gout are also seen and often become worse with stress. Patients may have a fixed second heart sound over the pulmonic area and a variety of cardiac murmurs. Biventricular hypertrophy and failure may also be present.

The definitive treatment of ES is a combined heart and lung transplant. The natural history of ES is slow progression over many years. Once heart failure or a rise in hematocrit above 60% occurs, prognosis is poor. Because the lung vessels are damaged by the high pressures and hypoxemia, cardiac transplant alone is not sufficient for success. ES is the most common indication for combined heart-lung transplant.[5]

Unfortunately, women with ES often have few symptoms until they become pregnant. The mortality of ES in pregnancy approaches 50% and appears to remain this high with each subsequent pregnancy.[6] Although compromised patients tend to have poor outcomes, good functional status prior to pregnancy is not necessarily protective. The highest risk of mortality appears to be in the immediate postpartum period.[7] The clinical deterioration seen is usually associated with sudden changes in existing shunts secondary to postpartum blood loss, pulmonary embolism, and inability of the pulmonary vasculature to adjust to the increased intravascular volume normally seen with pregnancy and delivery. Management of these patients usually consists of careful fluid and blood pressure monitoring and a controlled, stress-free, planned delivery.[8] The risk of placing a pulmonary artery catheter in a representative of this population may outweigh the benefits. The incidence of pulmonary artery rupture may be higher because of pre-existing pulmonary hypertension.[9] Additionally, the arrhythmias induced by pulmonary artery catheters[6] may further decrease cardiac output and pulmonary blood flow.[10,11] Although still controversial, anticoagulation should always be considered to help minimize the risk of thromboembolism.

This patient was admitted for early delivery because of worsening cardiac status. She experienced an uneventful early postoperative course but several days later developed hypoxemia. Her hypoxemia was thought to be due to the intraoperative blood loss that resulted in a decrease in CVP and thus increased intracardiac shunt. When the initial fluid resuscitation was unsuccessful in improving her hypoxemia, a chest radiograph was obtained that showed RUL collapse. This case illustrates that even in the complicated patient, simple problems are still common and should not be overlooked. Conservative management resulted in improved oxygenation. The patient and her baby continued to do well and were discharged home. When and if her symptoms worsen (increased hematocrit and heart failure), combined heart-lung transplantation will be considered.

REFERENCES

1. Stiller K, Geake T, Taylor J, Grant R, Hall B. Acute lobar atelectasis: a comparison of two physiotherapy regimens. Chest 1990;98(6):1336-1340.
2. AARC. Clinical practice guideline: nasotracheal suctioning. Respir Care 1992;37(8):898-901.
3. Strafford M. Transposition of the great vessels. In: Lake CL, ed. Pediatric cardiac anesthesia. New York: Appleton & Lange, 1988:229-241.

4. Wood P. The Eisenmenger syndrome of pulmonary hypertension with reversed central shunt. Br Med J 1958;2:701-709.
5. McGregor CGA, Jamieson SW, Baldwin JC, Burke CM, Dawkins KD, Stinson EB, et al. Combined heart-lung transplantation for end-stage Eisenmenger's syndrome. J Thorac Cardiovasc Surg 1986;91(3):443-450.
6. Lieber S, Dewilde P, Huyghens L, Traey E, Gepts E. Eisenmenger's syndrome and pregnancy. Acta Cardiol 1985;40(4):421-424.
7. Gleicher N, Midwall J, Hochberger D, Jaffin H. Eisenmenger's syndrome and pregnancy. Obstet Gynecol Surg 1979;34(10):721-741.
8. Pollack KL, Chestnut DH, Wenstrom KD. Anesthetic management of a parturient with Eisenmenger's syndrome. Anesth Analg 1990;70(2):212-215.
9. Hannan AT, Brown M, Bigman O. Pulmonary artery catheter-induced hemorrhage. Chest 1984;85(1):128-131.
10. Sprung CL, Pozen RG, Rozanski JJ, Pinero JR, Eisler BR, Castellanos A. Advanced ventricular arrhythmias during bedside pulmonary artery catheterization. Am J Med 1982;72(2):203-208.
11. Sprung CL, Jacobs LJ, Caralis PV, Karpf M. Ventricular arrhythmias during Swan-Ganz catheterization of the critically ill. Chest 1981;79(4):413-415.

American Association for Respiratory Care
40th Annual Convention and Exhibition
December 10-13, 1994 • Las Vegas, Nevada

Drugs for Pulmonary Mycoses

Hugh S Mathewson MD

Introduction

The incidence of opportunistic infections grows apace with the increasing number of immunocompromised patients. To the population of transplant recipients and those on cancer chemotherapy are now added the steadily rising number of patients with AIDS, contracted in a global pandemic now entering its second decade. The rising incidence of tuberculosis reflects this epidemiologic trend and illustrates the inadequacy of our therapeutic resources. A similar scenario has developed with the group of pulmonary and systemic diseases caused by fungi, known collectively as *mycoses*. Although primary systemic fungal infection does occur, most generalized mycoses are opportunistic, occurring as the result of failure of host immunity. In patients on cytotoxic drugs, the main problem is neutropenia, whereas in AIDS patients the defect is a loss of T-helper (or CD-4) cells. Effective antifungal chemotherapy must be prolonged to prevent relapse, and in many cases must be extended indefinitely. Each year drug-resistant strains of fungi appear and new species are identified, compounding the uncertainties of drug management.

The chemotherapy of mycoses is seriously limited by a paucity of available drugs. Amphotericin B, considered the most effective systemic antifungal agent since its introduction in the late 1950s, has severe dose-limiting toxicity and variable efficacy; flucytosine, which appeared a few years later, is characterized by a narrow spectrum, rapid emergence of resistance, and serious toxic side effects. Since 1980, when ketoconazole was introduced, pharmaceutical researchers have focused on the group of compounds collectively known as *azoles* (Fig. 1). These contain one or more 5-membered heterocyclic rings incorporating either two or three nitrogen atoms. Those with 2-nitrogen heterocycles are known as *imidazoles*, those with 3-nitrogen heterocycles are termed *triazoles*. They can be given orally, unlike amphotericin B. Fluconazole and itraconazole, both bi-triazoles, have been increasingly employed for systemic mycoses, and a newer derivative, saperconazole, will probably be approved in this decade. The clinical status of the azoles has been summarized in a number of recent reviews.[1-6]

Nearly all recently developed drugs are expensive, and the long-continued administration that many patients with systemic mycoses require presents formidable cost-containment problems. This article summarizes the present position of each of these drugs.

Dr Mathewson is Professor Emeritus of Anesthesiology and Professor of Respiratory Care Education—University of Kansas Medical Center, Kansas City, Kansas.

Reprints: Hugh S Mathewson MD, University of Kansas Medical Center, #5040-D, 39th & Rainbow, Kansas City KS 66103.

Antifungal Compounds

Table 1 lists the common mycotic diseases that affect the lungs and the current agents of choice. A discussion of new antifungal compounds, most of them in the preclinical stage of development, is also presented.

Amphotericin B

Amphotericin B is a macrolide antibiotic that belongs to the pharmacologic category known as polyenes (Fig. 2); the topical agent nystatin is also in this group. Polyene antibiotics bind to ergosterol in the membranes of fungal cells, causing pore formation and irreversible damage. Amphotericin B also binds, unfortunately, to cholesterol, which is present in many animal cell membranes. This probably accounts in part for its viscerotoxicity. For treatment of systemic fungal infections, it is given by slow intravenous infusion over 4-6 hours. Administration by this route usually produces chills, fever, vomiting, and headache. The drug impairs renal and hepatocellular function and suppresses hematopoiesis. Shocklike episodes, electrolyte disturbances, and neurologic symptoms are common. Renal tubular damage is so frequent that the drug may be impossible to use in the patient with pre-existing kidney disease.[7]

Amphotericin B has been reformulated in attempts to maintain a therapeutic serum level and reduce toxicity. A desoxycholate conjugate (Fungizone) has been used successfully for systemic candidiasis and as-

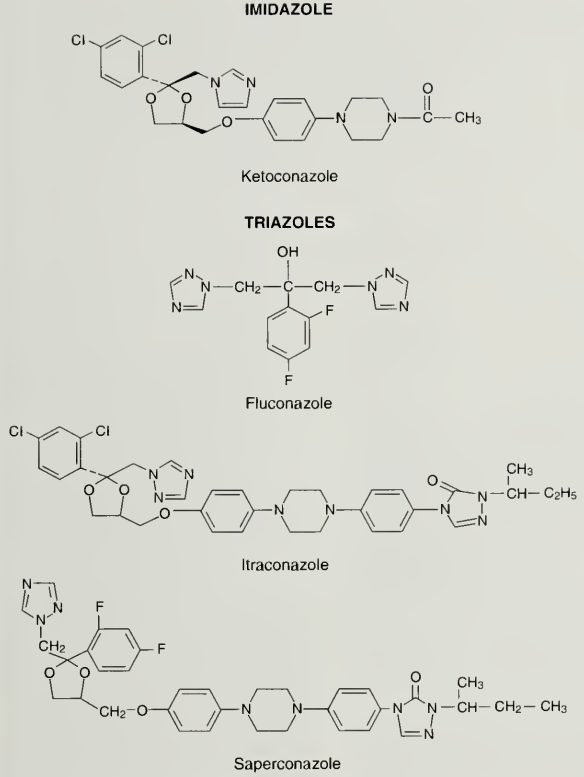


Fig. 1. Azole antifungal agents used for treatment of systemic mycoses.

pergillosis, but still has limited use in therapy. Preparations of the drug with lipid complexes or incorporation into liposomes have been given clinical trials as delivery systems.[8] Combined therapy with other antifungal drugs has been explored to reduce amphotericin toxicity. However, the drug has set a standard for efficacy that only recently has begun to be approached by newer antifungal agents, although it has major therapeutic gaps and the results of treatment have been variable and unpredictable.

Flucytosine

Flucytosine [9] is an antifungal drug, closely related to fluorouracil and floxuridine, used in cancer chemotherapy (Fig. 2). Only those fungal strains that convert flucytosine to fluorouracil are susceptible. The latter compound inhibits thymidylate synthetase and DNA synthesis. This biotransformation does not occur in mammalian cells, and flucytosine is thus relatively less toxic. However, prolonged high serum levels can cause bone marrow depression, hair loss, and altered liver function. Drug resistance secondary to the selection of nonsusceptible mutants occurs often and is an important cause of therapeutic failure. The drug is now rarely used alone for treatment of systemic mycoses.

Imidazoles

A number of synthetic imidazole derivatives were advanced as antifungal agents in the 1970s and 1980s. These compounds were found to inhibit fungal growth by blocking the synthesis of certain lipids in their cell membranes, notably ergosterol. All of them inhibit the enzyme C-14 lanosterol demethylase[10] but have different effects on other enzymes affecting sterol synthesis. Most of them can be used only topically (eg, clotrimazole, miconazole) because of serious systemic toxic properties. Ketoconazole (1981) was the first imidazole derivative to be introduced that could be given orally for extended periods. This drug revolutionized antifungal therapy, especially for the treatment of histoplasmosis, blastomycosis, and paracoccidioidomycosis.[3,5]

Ketoconazole causes some dose-dependent nausea, although taking it with food or at bedtime improves tolerance. It inhibits steroid biosynthesis, as it does in fungi, by inhibition of cytochrome P_{450}-dependent enzyme systems. Several endocrinologic abnormalities have been reported, largely related to disorders of estrogen, androgen, and corticosteroid synthesis.[11,12] With the appearance of triazole derivatives, the use of ketoconazole has declined, and interest has waned in further investigation of imidazole derivatives.

Triazoles

Fluconazole was approved for use in the USA in 1990.[13] It is more water soluble and more readily absorbed from the gastrointestinal tract than ketoconazole. Although it can be given either orally or parenterally, it is almost equally efficacious given by either route, as reflected by its serum levels. It has offered a reasonably effective alternative to amphotericin B for treatment of systemic candidiasis,

Table 1. Drugs of Choice for Common Systemic Mycoses

Mycosis	First Options	Investigational Drugs
Aspergillosis	Amphotericin B (liposomal)	Itraconazole Saperconazole
Blastomycosis	Itraconazole Ketoconazole Amphotericin B	
Candidiasis	Fluconazole Amphotericin B/flucytosine	Itraconazole
Coccidioidomycosis	Amphotericin B Ketoconazole	Fluconazole Itraconazole Saperconazole
Cryptococcosis	Amphotericin B/flucytosine	Fluconazole Itraconazole
Histoplasmosis	Itraconazole Amphotericin B Ketoconazole	Saperconazole
Paracoccidioidomycosis	Itraconazole Amphotericin B Ketoconazole	Saperconazole
Sporotrichosis	Itraconazole Amphotericin B	Saperconazole

and can suppress cryptococcal meningitis in AIDS patients, an important therapeutic breakthrough.[14] Compared to the older antifungal agents, its toxic properties are mild, consisting mostly of gastrointestinal disturbances, skin rashes, and sometimes hepatic dysfunction.

Itraconazole, a triazole structurally related to ketoconazole, has recently (1992) become available in oral form, and may offer a broader spectrum of antifungal activity, particularly against aspergillosis.[15-17] While fluconazole is largely excreted unchanged, itraconazole (like ketoconazole) is extensively metabolized. However, itraconazole is much the longer acting of the two, with a half-life of 24 to 42 hours, compared to 7 to 10 hours for fluconazole. The triazoles do not inhibit steroidogenesis, a problem encountered with ketoconazole. Fluconazole has little effect on the immune system, whereas itraconazole is definitely immunosuppressive. Saperconazole, a newer triazole compound, has undergone clinical trials and shows a broad spectrum of antifungal activity.[18-20] It is especially effective in candidiasis and cryptococcosis. It awaits the approval of the U.S. Food and Drug Administration (FDA).

Investigational Antifungal Compounds

New chemicals proposed for trial as antifungal agents must first be tested in vitro. Antifungal susceptibility testing is not uniformly standardized, with the result that correlations between in-vitro results and responses in animal models are often conflicting. A number of compounds that appeared promising in the microbiology laboratory have been found wanting in subsequent animal studies. Of even more disturbing significance, clinical failures have occurred where in-vitro sensitivity studies have been strongly positive. It has been suggested that triazoles not be tested in vitro.[21] Work is in progress to establish uniform susceptibility testing of yeasts. It is less certain that correlations between in-vitro and in-vivo responses will soon be developed for many mycoses, especially those due to molds. Development of antifungal drugs of clinical worth will be problematic until this can be accomplished.[22]

There is limited interest in further development of polyenes. New lipid formulations of amphotericin B, nystatin, and a related compound, hamycin,[23] are under investigation, but it is likely that viscerotoxic properties will prevent their widespread acceptance for any but the most life-threatening mycoses. New azoles include saperconazole, mentioned earlier, which is in the clinical trial period. The study of a very promising triazole, SCH 39304, was interrupted when carcinogenic properties were manifested in rodents.[2,24] Formulations with beta-cyclodextrins as carriers will enable new azoles to be given intravenously.[25]

Finding a biochemical target in fungi other than sterol synthesis now occupies a number of research efforts, some particularly directed toward control of candidiasis. Certain lipopeptides, the best known of which is cilofungin (LY121019), protects against Candida by interfering with synthesis of an intermediary metabolite, 1,3-beta-D-glucan.[24] A number of families of cytotoxic antibiotics (sampangines,[26] pradimicins,[27] and others[2]) have provided compounds with antifungal properties. They show general cytotoxicity, creating interest for their investiga-

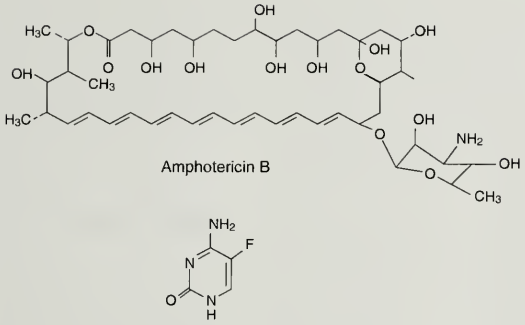


Fig. 2. Early generation systemic antifungal drugs.

tion as anticancer drugs, but they lack specificity for fungi. Their in-vitro activity against *C. albicans* is one test commonly employed to determine whether further studies are warranted.

With the exception of saperconazole, it appears unlikely that any new systemic antifungal agents will be released before the end of the decade. However, the urgency of treatment of systemic mycoses in AIDS patients may accelerate FDA release of selected compounds of demonstrated efficacy. For neutropenic patients on cancer chemotherapy, there is now considerable interest in biologic products to reduce immunodeficiency. These include granulocyte-macrophage colony-stimulating factor, recombinant human cytokines, and transfusable preparations of effector cells.

In Summary

Systemic mycoses are part of a growing public health problem. Diagnosis in immunocompromised patients may not be evident until the disease has become untreatable. It may be reasonable to administer antifungal drugs prophylactically to neutropenic or CD-4 deficient patients. Recent studies of antifungal prophylaxis in patients with neoplastic diseases have been summarized in a recent report.[28] One uncontrolled study of interest involved the use of aerosolized amphotericin B for prevention of aspergillosis.[29]

The costs of drug prophylaxis can be exorbitant because many of these patients will be on an antifungal drug regimen for life. Screening methods to identify mycoses in their formative periods are urgently needed. Early aggressive drug treatment may save lives that might otherwise be lost waiting for a response to anticancer chemotherapy. Whether these therapeutic efforts can be sustained depends on more accurate selection of patients, and on the development of novel antifungal drugs to combat resistant organisms. This is a formidable future assignment imposed on the medical community and on pharmaceutical researchers.

REFERENCES

1. Hay RJ. Antifungal therapy and the new azole compounds. J Antimicrob Chemother 1991;28(Suppl A):35-46.
2. Lyman CA, Walsh TJ. Systemically administered antifungal agents: a review of their clinical pharmacology and therapeutic applications. Drugs 1992;44(1):9-35.
3. Graybill JR. Future directions of antifungal chemotherapy. Clin Infect Dis 1992;14(Suppl 1): S170-S181.
4. Bodey GP. Azole antifungal agents. Clin Infect Dis 1992;14 (Suppl 1):S161-S169.
5. Terrell CL, Hughes CE. Antifungal agents used for deep-seated mycotic infections. Mayo Clin Proc 1992;67(1):69-91.
6. Como JA, Dismukes WE. Oral azole drugs as systemic antifungal therapy. N Engl J Med 1994;330 (4):263-272.
7. Gallis HA, Drew RH, Picard WW. Amphotericin B: 30 years of clinical experience. Rev Infect Dis 1990;12(2):308-329.
8. Schmitt H-J. New methods of delivery of amphotericin B. Clin Infect Dis 1993;17(Suppl 2):S501-S506.
9. Francis P, Walsh TJ. Evolving role of flucytosine in immunocompromised patients: new insights into safety, pharmacokinetics, and antifungal therapy. Clin Infect Dis 1992;15(6):1003-1018.
10. Joly V, Bolard J, Yeni P. In vitro models for studying toxicity of antifungal agents. Antimicrob Agents Chemother 1992;36(9):1799-1804.
11. Loose DS, Kan PB, Hirst MA, Marcus RA, Feldman D. Ketoconazole blocks adrenal steroidogenesis by inhibiting cytochrome P_{450}-dependent enzymes. J Clin Invest 1983;71(5):1495-1499.
12. Pont A, Graybill JR, Craven PC, Galgiani JN, Dismukes WE, Reitz RE, Stevens DA. High-dose ketoconazole therapy and adrenal and testicular function in humans. Arch Intern Med 1984;144(11):2150-2153 .
13. Galgiani JN. Fluconazole, a new antifungal agent. Ann Intern Med 1990;113(3):177-179.
14. Grant SM, Clissold SP. Fluconazole: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial and systemic mycoses. Drugs 1990;39(6):877-916.
15. Grant SM, Clissold SP. Itraconazole: a review of its pharma-

codynamic and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. Drugs 1989;37(3):310-344.
16. Sharkey PK, Rinaldi MG, Dunn JF, Hardin TC, Fetchick RJ, Graybill JR. High-dose itraconazole in the treatment of severe mycoses. Antimicrob Agents Chemother 1991;35(4):707-713.
17. Dismukes WE, Bradsher RW Jr, Cloud GC, Kauffman CA, Chapman SW, George RB, et al. Itraconazole therapy for blastomycosis and histoplasmosis: NIAID Mycoses Study Group. Am J Med 1992; 93(5):489-497.
18. Saag MS, Dismukes WE. Azole antifungal agents: emphasis on new triazoles. Antimicrob Agents Chemother 1988;32(1):1-8.
19. Van Cutsem J, Van Gerven F, Janssen PAJ. Oral and parenteral therapy with saperconazole (R66905) of invasive aspergillosis in normal and immunocompromised animals. Antimicrob Agents Chemother 1989;33(12):2063-2068.
20. Franco L, Gomez I, Restropo A. Treatment of subcutaneous and disseminated mycoses with saperconazole (abstract PS 3.99). In: Proceedings of the 11th Congress of the International Society of Human and Animal Mycology. Leeds UK: International Society for Human and Animal Mycology, 1991.
21. Kobayashi GS, Spitzer ED. Testing of organisms for susceptibility to triazoles: is it justified? Eur J Clin Microbiol Infect Dis 1989; 8(5):387-389.
22. Galgiani JN. Susceptibility testing of fungi: current status of the standardization process. Antimicrob Agents Chemother 1993;37(12): 2517-2521.
23. Mehta RT, McQueen TJ, Keyhani A, Lopez-Berestein G. Liposomal hamycin: reduced toxicity and improved antifungal efficacy in vitro and in vivo. J Infect Dis 1991; 164(5):1003-1006.
24. Barrett JF, Klaubert DH. Recent advances in antifungal agents. Ann Rep Med Chem 1992;27:149-158.
25. Hostetler JS, Hanson LH, Stevens DA. Effect of cyclodextrin on the pharmacology of antifungal oral azoles. Antimicrob Agents Chemother 1992;36(2):477-480.
26. Liu S, Oguntimein B, Hufford CD, Clark AM. 3-Methoxysampangine, a novel antifungal copyrine alkaloid from *Cleistopholis patens*. Antimicrob Agents Chemother 1990;34(4):529-533.
27. Oki T, Tenmyo O, Hirano M, Tomatsu K, Kamei H. Pradimicins A, B and C: new antifungal antibiotics. II. In vitro and in vivo biological activities. J Antibiot Tokyo 1990;43(7):763-770.
28. Walsh TJ, Lee JW. Prevention of invasive fungal infections in patients with neoplastic disease. Clin Infect Dis 1993;17(Suppl 2): S468-S480.
29. Conneally E, Cafferkey MT, Daly PA, Keane CT, McCann SR. Nebulized amphotericin B as prophylaxis against invasive aspergillosis in granulocytopenic patients. Bone Marrow Transplant 1990; 5(6):403-406.

American Association for Respiratory Care
40th Annual Convention and Exhibition
December 10-13, 1994 • Las Vegas, Nevada

RETROSPECTROSCOPE REDUX:

"Tell It Like It Was"

In the first article of this series,[1] I wrote that I did not intend to use the Retrospectroscope to uncover who did what before whom, but rather to analyze how and why important discoveries (and sometimes rediscoveries) came about. I can tell you unequivocally that it's a hard job—largely because of the rigid format and style of the modern scientific article. Scientists presumably spend a lifetime in science because of the joy of discovery, but this joy rarely comes through to the reader of their scientific articles. Worse, for those seriously interested in learning more about the process of scientific discovery, the scientist, once he changes into the role of author, rarely "tells it like it was"; he conforms to the IMRAD) style—Introduction (concise and impersonal) Methods, Results And Discussion—and leaves out, "Why did I do it? Was my initial idea right or wrong? How did I get on the right track?"

Schilling, in an article published in 1958[2] laid it on the line in his subtitle: "Science as Lived by Its Practitioners Bears but Little Resemblance to Science as Described in Print." He then went on to say:

> ... the findings of science are usually presented to students and the public as straightforward, logical developments, rather than in such a way as to reveal how they actually evolved—haltingly, circuitously, with many false starts, and often even illogically. While there are, of course, very good reasons for this, the fact is that, in the absence of further explanation, it leaves the uninitiated with a thoroughly misleading idea of the processes of science.

Six years later, Medawar also took scientists to task for *doing* their research one way, and *telling* it another way.[3] In his "Is the Scientific Article Fraudulent? Yes; It Misrepresents Scientific Thought" he writes:

> ... I do not, of course, mean "Does the scientific paper misrepresent facts?" and I do not mean that the interpretations you find in a scientific paper are wrong or deliberately mistaken. I mean the scientific paper may be a fraud because it misrepresents the processes of thought that accompanied or gave rise to the work that is described in the paper.
>
> That is the question, and I will say right away that my answer to it is "yes." The scientific paper in its orthodox form does embody a totally mistaken conception, even a travesty, of the nature of scientific thought. ...

Once in a while, a scientist does tell us, in his initial report, how he came upon his discovery. Roentgen did (see "The Inside Story"[4]). So did Sidney Ringer (forever famous for Ringer's solution), whose discovery of the essential role of calcium and potassium in normal cardiac contraction and rhythm was all-important to much of today's basic and clinical research on the heart.

Calcium and Cardiac Contraction

How did Ringer make his celebrated discovery? Here are his words in the 1883 *Journal of Physiology*:[5]

> After the publication of a paper in the *Journal of Physiology*, Vol III, No 5, entitled "Concerning the influence exerted by each of the Constituents of the Blood on the Contraction of the Ventricle," I discovered that the saline solution which I had used had not been prepared with distilled water, but with pipe water supplied by the New River Water Company. As this water contains minute traces of various inorganic substances, I at once tested the action of saline solution made with distilled water and I found that I did not get the effects described in the paper referred to. It is obvious therefore that the effects I had obtained are due to some of the inorganic constituents of the pipe water.
>
> Water supplied by the New River Water Company contains 278.6 parts of solids per million.

Reprinted, with permission of the American Lung Association, from Am Rev Respir Dis 1976;113:667-676.

[The actual total of the solids listed is 283.5 parts per million.]

They consist of:

Calcium	38.3	per million
Magnesium	4.5	"
Sodium	23.3	"
Potassium	7.1	"
Combined Carbonic Acid	78.2	"
Sulphuric Acid	55.8	"
Chlorine	15	"
Silicates	7.1	"
Free Carbonic Acid	54.2	"

This water is faintly alkaline to test-paper from bicarbonate of lime. Saline made with this water I found at first rounds the top of the trace of each contraction and later greatly prolongs diastolic dilatation, and that these effects are completely obviated by about 1 cc of 1% solution of potassium chloride solution to the 100 cc of circulating saline. So that with this addition the saline thus made forms an excellent artificial circulating fluid for the heart, as in some experiments I found the ventricle fed by this mixture would continue beating well for more than four hours, indeed at the end of that time the contractions were almost as good as at the commencement of the experiment, when the ventricle was fed with blood mixture. . . .

The heart's contractility cannot be sustained by saline solution nor by saline containing potassium chloride, nor with saline solution containing bicarbonate of soda, nor by saline solution containing bicarbonate of soda and potassium chloride; but after contractility has ceased, the addition of a lime salt will restore good contractility. The addition too of a calcium salt to any of the above solutions will sustain contractility. I conclude therefore that a lime salt is necessary for the maintenance of muscular contractility. . . .

If these two salts are not present in the correct proportions then the trace becomes abnormal. If too little potassium is present, the contractions become broader etc. and there results fusion of the beats. If too much potassium is present, or too little lime salts, then the contraction of the ventricle is imperfect, and by increasing the quantity of potassium salt the beat becomes weaker and weaker till it stops.

Ringer's account gives me the picture of a man puzzled by the results of his earlier experiments, unwilling to accept them, and checking every possible error in technic. He found the error and at once identified the important role of calcium ions in cardiac function. A conventional paper by Ringer would have given us *calcium* but not the important lesson to all future scientists: check the composition and purity of all reagents.

Protamine-Heparin Antagonism

Chargaff and Olson told it "like it was" when they discovered a new action of protamine in 1937:[6]

> . . . the animal organism seems able to dispose of it [heparin] in a comparatively short time. Whether this is brought about by rapid combination of the heparin with the proteins of the tissues or of blood, by its excretion, or by its destruction, it is not yet established. We have attempted to protract the short lived activity of heparin by combination with a protamine, *viz.* salmine. This was done in view of the promising results obtained with the combination of insulin and protamine: In the case of heparin the effect was unexpected: the anticoagulant action of heparin *in vivo* was entirely stopped by protamine. The significance of these findings and some possible practical applications will be discussed later in this paper. . . .

Their hypothesis, although quite reasonable, was wrong; their result, although totally unexpected, turned out to be of considerable clinical importance. Because editors forever remind us that paper, printing, binding, and mailing are all very expensive, it's important to note that Chargaff and Olson took only 56 words—well worth it—to tell scientists that the *un*expected may sometimes be worth more than the expected result.

The Discovery of Heparin

A lot of scientists have told us, several decades later, how it really happened at the time of their initial discovery.

One of these was Jay McLean, who discovered heparin in 1916 but didn't "tell it like it was" until 1957. Indeed, in 1916 he scarcely told anything at all; neither the title of his article, "The Thromboplastic Action of Cephalin," nor his conclusions mention his discovery of heparin or of a new anticoagulant.[7] Here are excerpts from his initial article. All of its 8 pages deal with factors that *hasten* blood coagulation (thromboplastic factors), except for 4 lines on p 256 that mention a new anticoagulant!

> In 1912 Howell reported the results of a study of the Thromboplastic action of the tissues in which he showed that the active substance is a phosphatid having the general properties of cephalin. . . . At the suggestion of Dr Howell I have undertaken a re-exami-

nation of this subject to determine if possible whether the thromboplastic effect may be attributed to an impurity, or is a property of the cephalin itself, and also to determine in how far a similar property is exhibited by other related phosphatids. The phosphatids which have been examined in regard to their thromboplastic action are cephalin, lecithin, sphingomyelin, cuorin and heparphosphatid.

[McLean then described his preparation of laboratory cephalin, of cephalin prepared by the method of Renall and by the method of Levene and West, and of cephalin and cuorin from the heart. He then described the preparation of cephalin and heparphosphatid from the liver.]

Baskoff, in his work on the phosphatids of the liver, undertaken primarily for the study of the jecorin described by Drechsel, succeeded in isolating a phosphatid which resembles cuorin, except that analysis shows a N:P ratio of 1:1.5 instead of 1:2. To this phosphatid he gave the name of heparphosphatid. In my experiments the liver was worked up according to Baskoff's method for obtaining heparphosphatid which is practically the same treatment to which Erlandsen subjects the heart muscle in order to secure his cuorin. The final substance insoluble in cold alcohol was further divided into a fraction insoluble in alcohol at 60° which resembles cuorin and constitutes Baskoff's heparphosphatid, and a portion soluble in alcohol at 60° which is apparently identical with cephalin. When the latter was recovered from the alcoholic solutions as in the case of the cephalin of the heart, it had all of the general properties of cephalin including the power to hasten the coagulation of blood as is shown in this experiment.

Using—Plasma, 8 drops; cephalin, 3 drops; serum, 3 drops.

Control—Plasma, 8 drops; water, 3 drops; serum, 3 drops.

Liver cephalin . . . . . solid clot 1½ min.
Laboratory cephalin . . . . solid clot 1½ min.
Control . . . not clotted in 1 hour and 45 min.

The heparphosphatid on the other hand when purified by many precipitations in alcohol at 60° has no thromboplastic action and in fact shows a marked power to inhibit the coagulation. The anticoagulating action of this phosphatid is being studied and will be reported upon later. [Italics added] Cuorin and heparphosphatid when dry have no odor, but when moist with warm alcohol have a characteristic odor common to both. It is possible that on further purification the heparphosphatid may he shown to be identical with cuorin. . . .

CONCLUSIONS

1. Cephalin when prepared as pure as possible exhibits marked thromboplastic activity, as indicated by its effect in increasing the thrombic action of fresh serum.

2. Cephalin exhibiting this reaction has been prepared from the liver, heart and brain.

3. The other phosphatids that have been described, lecithin, cuorin, heparphosphatid and sphingomyelin have no thromboplastic action.

4. Evidence is presented to show that this property of cephalin is not due to adherent impurities, but is a characteristic property of the cephalin itself.

In 1957, shortly before his death, McLean recounted the actual story.[8] McLean was a University of California undergraduate student at Berkeley, with his heart set on going to Johns Hopkins Medical School. He worked for two years, saved his money, applied for admission and was turned down. That didn't stop him and he made his way from California to Baltimore and to the Dean's Office. The Dean told him he could accept him the next year, so McLean decided to spend the year doing research. Here are parts of his story:

I promptly paid the fees for a year as a medical student, taking no medical school courses. I immediately called on Dr Howell and told him of my desire to prepare for an academic career in surgery and that I wished to devote one whole year to physiological research now. I felt that I could never do it after graduation for that would interfere with the house officer progress on a surgical staff. I told him then that I wanted a problem I could reasonably hope to finish and publish in one academic year entirely by myself. I wanted to determine if I could solve a problem by myself. I told him my savings would just last one year, and after that I would have to work a year before returning to school.

He gave me the problem of determining the value of the thromboplastic substance of the body. He thought this to be kephalin (cephalin), obtained from brain but, of course, knew the thromboplastic material from brain to be a mixture—a crude extract, though a powerful thromboplastic agent. . . .

My problem was to determine what portion of this crude extract was the active accelerator of the clotting process and to that end, to prepare cephalin as pure as possible and determine if it had thromboplastic action. I was also to test the other components of the crude ether-alcohol extract. . . .

It was this determination to become a physiology-based surgeon rather than an anatomy-based surgeon that led to the discovery of heparin. . . . I suggested to Dr Howell that it might be profitable to extract the lipoids (phosphatides) from many different

organs. . . . In my reading of the German chemical literature on phosphatides, I found articles by Erlandsen and Baskoff in which they described extracts of heart and liver secured by a process similar to that for obtaining cephalin from brain. Therefore, these products might be heart and liver cephalin, but were named cuorin (from the heart) and heparphosphatide (from the liver); hence the name heparin. I suggested this research problem as a logical supplement to the problem Dr Howell had given me. He had not known about cuorin or heparphosphatide. . . . I had saved batches of cuorin and heparphosphatide and from time to time tested these in serum plasma to determine whether or not the cephalin from the heart and liver deteriorated and lost its thromboplastic power as did that from the brain. If I had not saved them, I would probably not have found heparin. . . .

The various batches were tested down to the point of no thromboplastic activity, but two of those first prepared appeared not only to have lost their thromboplastic action, but actually to retard slightly the coagulation of the serum-plasma mixture. I had in mind, of course, no thought of an anticoagulant, but the experimental fact was before me; and I retested again and again until I was satisfied that an extract of liver (more than heart) possessed a strong anticoagulant action after its contained cephalin had lost its thromboplastic action.

I went one morning to the door of Dr Howell's office, and standing there (he was seated at his desk) said, "Dr Howell, I have discovered antithrombin." He smiled and said, "Antithrombin is a protein and you are working with phosphatides. Are you sure that salt is not contaminating your substance?"

I told him I was not sure of that, but it was a powerful anticoagulant. He was most skeptical. So I had the Diener, John Schweinhart, bleed a cat. Into a small beaker full of its blood, I stirred all of a proven batch of heparphosphatides, and I placed this on Dr Howell's laboratory table and asked him to tell me when it clotted. It never did clot.

He still did not believe that I had discovered a natural anticoagulant, but it was at this point that he became associated in my research problem, namely the study of the effects of my anticoagulating substance (heparphosphatide), which gave greater yield and higher coagulating potential than cuorin *in vivo* in dogs. When I demonstrated new batches to him *in vitro,* and he became satisfied that it did actually inhibit the coagulation of the serum-plasma test mixture as well as whole blood *in vitro,* we planned the first *in vivo* experiment with a dog and administered the heparin intravenously.

[This was as far as Dr McLean progressed in his history of the discovery of heparin before he developed his fatal illness and died November 14, 1957—Ed.]

One learns more about the process of scientific discovery from the 1957 account than from the 1916 article. One learns how important it was for science that the Professor (Howell) gave an inexperienced student a free hand to make mistakes or discoveries. One learns how important it was that the student explored his unexpected and contradictory observations instead of ignoring them. And how important it was that he convinced his doubting professor that, with heparin added, the blood "never did clot"!

Citrate as an Anticoagulant

It's pretty hard, in 1976, to realize that between 1900 and 1915 the accepted method for giving a blood transfusion was to anastomose, by a long and delicate surgical procedure, the artery of a donor to the vein of the patient. There were no indirect transfusions because there was no way to keep blood liquid outside of the body except by defibrinating it (by whipping it with broomstraws) and defibrinated blood often caused serious reactions. In 1914, a young Belgian physician, Dr Hustin, found that when sodium citrate was added to blood, blood stayed liquid long enough to permit indirect transfusion.

Why did Hustin use citrate? Here are excerpts from his coinventional 1914 paper[9] (my translation from his French):

> Blood transfusion, the introduction of blood from one individual into the circulation of another, is a very old therapeutic technic which has been revived in the last few years by the efforts of the American surgeon, Crile. . . .
>
> For two centuries, physicians have tried to join vessels of a donor directly to those of the recipient. But the failures of this method were numerous because the tubes used to join the vessel provoked clotting of the blood and obstruction of the tube. In the past several years experiments with suturing vessels have demonstrated the importance of the endothelial lining and the role played by tissue juices in blood coagulation. . . . New technics of vascular suture give good results but they present numerous problems: they require a longer and very delicate operation; an imperfection in one step may often lead to total failure of the procedure; there is no certain way of measuring the amount of blood transfused at any given time, except for the overall condition of the donor and recipient . . . the need to bring the vessels of the donor and recipient into direct contact increases the donor's chance of being infected by the recipient: because of the complexity of the technic, one must obtain from one donor the entire

quantity of blood needed and transfuse it all at once . . . in spite of precautions, clots can form at the site of the anastomosis and either stop blood flow there or be dislodged into the circulation. . . .

[Hustin then discussed two ways of delaying blood coagulation. One was to decrease the concentration of electrolytes in blood by adding isotonic sodium chloride, Ringer's, or glucose solution; possibly these acted to dilute the calcium concentration of the blood. The other was to add "dispersing substances," particularly sodium citrate. His table (**see below**) showed that blood plus isotonic glucose plus citrate kept blood from clotting for as long as 45 to 67 minutes (line 8) compared with dilution only with salt solution (line 7) or with saline plus glucose (line 11). He then proceeded to transfuse citrated blood from dog to dog, rabbit to rabbit, man to dog, and finally man to man.]

The technic of the transfusion that I have described requires two steps. One allows a certain amount of venous blood to flow into an equal amount of isotonic glucose-citrate solution, by means of one or several venipunctures (about 150 mL of blood with each puncture from an average-sized vein). This liquid is then poured into ordinary serum apparatus; it is then injected into a vein after transcutaneous puncture. . . .

IN SUMMARY:

1. The technic of transfusion that we have used requires no complicated surgical operation but only several venipunctures.

2. It permits precise measurement of the quantity of blood transfused, a matter of great importance to the safety of the donor.

3. It eliminates transferring an infection from the patient to the donor.

4. One can transfuse as often as necessary; several donors can be used at the same time.

5. Between the time of collection and infusion, one can submit the blood to certain manipulations (removal of carbon monoxide and replacement with oxygen; different types of irradiation).

6. In many of the cases in which transfusion is indicated, the heart of the patient needs to be strengthened and glucose is known to be a nutrient of the first order for cardiac muscle fibers.

7. The delay in blood coagulation is long enough to permit a slow transfusion and so prevent overburdening the right heart.

In 1960, Hustin wrote another article on blood transfusion,[10] telling what had motivated his 1914 work and why he was successful. Here are his words (my translation from the French):

Pekelharing and Sabattini's physiological studies in 1902 were, for a long time, ignored by clinicians; at least not a single clinician had thought of using the anticoagulant properties of sodium citrate for blood transfusion. I was not even aware of its anticoagulant properties when, in 1913, I undertook my first attempts of blood transfusion in the Laboratory of Physiology at the University of Brussels. At that time, I knew only of Gengou's work—that sodium citrate had dispersing properties and rendered stable a suspension of mastic.

It was not by looking for a new method of transfusion that I conceived of the technique of transfusing citrated blood. If this had been my intention, it is probable that I would have followed the usual tracks and that I would have succeeded, at best, in improving on some procedure or some apparatus already known. My goal was quite different, as you will see.

Composition of the Mixture

		Coagulation Time	
		Beginning (minutes)	End (minutes)
1.	Blood + saline solution + 50 centigr. % citrate	12	15
2.	" + " + 40 "	5	13
3.	" + " + 30 "	5	15
4.	" + " + 20 "	5	15
5.	" + " + 10 "	4	22
6.	" + " + 5 "	–	9
7.	" + saline solution	4	8
8.	Blood + glucose solution + 50 centigr. % citrate	45	67
9.	" + " + 30 "	25	32
10.	" + " + 10 "	9	15
11.	" + glucose solution	–	12

It happened that one day, at the hospital, I found myself standing by a man dying from inhalation of illuminating gas. I told myself that one could save his life if only one could withdraw part of his blood, remove the carbon monoxide blocking its hemoglobin, and then reinject the withdrawn blood once it had been purified and properly oxygenated. But to achieve this plan of treatment, first it was necessary, after withdrawing blood from the patient, to maintain the blood in a fluid state during the time required to extract the toxic gas. It was at this moment that I realized the possibility of stabilizing the blood by means of sodium citrate, since this salt had demonstrated its property of maintaining mastic in suspension.

I then undertook "in vitro" attempts; first I had to make sure that sodium citrate acted on blood as it did on mastic; ie, that sodium citrate prevented it from becoming a gel; then I had to determine the amount of citrate needed for delaying blood coagulation for at least half an hour. ... For reasons that would be too long to report here, I also added glucose so I came to use a glucose-citrate mixture as my anticoagulant solution.

If, at that time, I had pursued my initial goal—that of saving patients intoxicated by carbon monoxide—I would have looked for some means of extracting the carbon monoxide contained in the blood. But I did not because I realized that my researches had led me, unintentionally, to an entirely new method of transfusion: the glucose-citrated transfusion. In order to reach this new objective, I had only to demonstrate that reinjection of blood, made uncoagulable by sodium citrate, could be performed without danger for the patient.

I then injected a dog with some citrated blood that had been withdrawn from another dog: thereafter I injected a dog with blood sampled from a human being; finally, on March 27, 1914, I performed at St John Hospital in Brussels, the first transfusion of glucose-citrated blood, from one man to another man.

One might wonder why transfusion with citrated blood was not discovered shortly after the discovery of anticoagulant properties of sodium citrate in 1896. One might further wonder since, at the beginning of the century, the dangers of transfusion had been overcome and the interest of the medical world in transfusion had been revived by the techniques that imaginative surgeons had devised to anastomose blood vessels. ... Without any doubt, particular circumstances in certain men's life have often played a role in their inventions or discoveries. The first circumstance was that, while acting as a surgeon at the hospital in 1910, I had undertaken experimental work on animals in the Physiological Laboratory of the University of Brussels. As part of this, I often had to withdraw from dogs a certain amount of blood which I had maintained in a fluid state by shaking it with glass beads, so that I could then perfuse it through the vessels of isolated organs. The concept of making blood incoagulable was then familiar to me. To treat carbon monoxide poisoning, I had to change only one thing: to replace the mechanical action of the glass beads by the chemical action of sodium citrate. The second circumstance was that my hospital activities had initiated me to the current problems associated with blood transfusion. So I was led to leave a problem of limited interest—the treatment of carbon monoxide intoxication—for a problem of much wider interest, that of blood transfusion.

The idea of citrated transfusion was then born quite naturally from a mind formed by two different disciplines, a physiological and a clinical one, the hospital environment raising the question to solve, the laboratory providing the elements for the answer.

Microvascular Surgery

One of the great cardiovascular advances was microvascular surgery, introduced by Jacobson and Suarez in a modest, conventional 2-page paper in 1960.[11] Here are some excerpts from it:

> Results of arterial surgery have been uniformly poor in vessels below 4 mm in diameter. The reason, it seems to us, is purely technical. A 1 mm error in suture placement results in thrombosis in a 2 mm anastomosis but has little significance when one works on large vessels.
>
> Techniques have been developed for performance of vascular anastomosis under the dissecting microscope. Far greater accuracy in suture placement is obtained. ... Bits of adventitia not visible to the naked eye can be removed. The surgeon can tie knots so that intimal edges almost exactly coapt.
>
> One hundred per cent patency rates have been found in the carotid arteries of 20 dogs and 6 rabbits observed up to 4 months. The vessels averaged 3.2 and 1.4 mm respectively. ...
>
> It is our belief that the techniques presented will extend vascular surgery to many previously inaccessible areas.

Clear and concise, but it doesn't tell *why*, after otologists had been operating with the aid of magnifying lenses and microscopes for almost 40 years, no vascular surgeon picked up the ball until 1960. I wrote to Jacobson in 1972 and he told me how it really happened (Jacobson, JH: Personal communication. Aug 7, 1972):

In 1959 I completed a seven-year residency at New York's Presbyterian Hospital and stayed on there for a short while as an attending surgeon. In 1960 I was appointed the Director of Surgical Research at the University of Vermont and was able to transfer a sizable USPHS grant entitled "Factors in the Development of Collateral Circulation." It was this money that allowed us to do the initial work in microsurgery.

Just before leaving Presbyterian Hospital, I wandered into one of the Ear, Nose, and Throat operating rooms and was allowed to look through the Zeiss microscope they were using. I'm sorry to say that there was no sudden recognition of its potential value in vascular surgery.

Some months later, on my arrival in Vermont, one of the pharmacologists asked for help in completely denervating the canine carotid artery. The only way to really accomplish this with certainty was to divide a segment of the vessel and re-anastomose the divided ends. In attempting to do this, it was immediately evident that the problem was not in the ability of the hand to do but rather the eye to see. Early experimentation was carried out using ocular loupes and large magnifying glasses placed over the operative field. These proved unsatisfactory for one reason or another and finally I remembered looking through the ENT microscope.

A Zeiss microscope was borrowed from the operating room and used in the performance of a small vessel anastomosis. The experience was very much like looking at the moon for the first time through a powerful telescope; a wealth of previously unappreciated detail was seen for the first time and minor surgical errors became glaringly apparent. I should add at this point that before going to medical school I had worked in the area of cell physiology under Dr LV Heilbrunn, and had also spent several summers at Woods Hole. I interject this because, in thinking back, it becomes obvious to me that I probably would not have attempted to interpose a microscope between my eyes and the surgical field had the use of dissecting microscopes not been second nature to me by that time.

One final question: Why did the Vermont pharmacologists want to study a denervated carotid artery? Here are a few lines from their 1962 paper:[12]

> Our present experiments . . . were designed to determine whether the altered sensitivity of the reserpine-treated and denervated tissues to nor-adrenaline, tyramine and nicotine was correlated with changes in the noradrenaline content of the artery. . . . Denervation of the artery was performed by two different methods: first, by arterial stripping; secondly, by removal and reversal of an arterial segment with subsequent anastomosis using the method described by Jacobson and Suarez (1960).

Now we know why microvascular surgery began in 1960. A surgeon, fascinated by research because of stimulating experiences at Woods Hole Biological Laboratories and with an inspiring general physiologist, Lewis Heilbrunn, was asked by two pharmacologists to lend his technical skill to help solve a basic problem on the sensitivity of denervated arteries. Conventional surgical technics then available to him were obviously inadequate but instead of his saying, "Sorry, it's impossible," he came up with microvascular surgery, which in turn led to many other new surgical methods for opening closed ducts or tubes, including re-opening a ligated vas deferens. We still don't know why a Jacobson didn't come along in 1930, 1940, or 1950. Maybe there wasn't anyone with the same combination of surgical research training, inquisitiveness, patience, and willingness to help a couple of basic scientists working on an esoteric problem.

Penicillin

In 1940, Chain and associates[13] published their first report on the chemotherapeutic action of penicillin in experimentally infected mice. The report essentially said that it was about time to study naturally occurring chemotherapeutic substances and the group started with a study of penicillin. Here are excerpts from this historic article, which was written in a fairly conventional format:

> In recent years interest in chemotherapeutic effects has been almost exclusively focused on the sulphonamides and their derivatives. There are, however, other possibilities, notably those connected with naturally occurring substances. It has been known for a long time that a number of bacteria and moulds inhibit the growth of pathogenic micro-organisms. Little, however, has been done to purify or to determine the properties of any of these substances. The antibacterial substances produced by *Pseudomonas pyocyanea* have been investigated in some detail, but without the isolation of any purified product of therapeutic value.
>
> Recently, Dubos and collaborators (1939, 1940) have published interesting studies on the acquired bacterial antagonism of a soil bacterium which have led to the isolation from its culture medium of bactericidal substances active against a number of gram positive micro-organisms. Pneumococcal infections in mice were successfully treated with one of these substances, which, however, proved to be highly

toxic to mice (Hotchkiss and Dubos 1940) and dogs (McLeod et al 1940).

Following the work on lysozyme in this laboratory it occurred to two of us (EC and HWF) that it would be profitable to conduct a systematic investigation of the chemical and biological properties of the antibacterial substances produced by bacteria and moulds. This investigation was begun with a study of a substance with promising antibacterial properties, produced by a mould and described by Fleming (1929). The present preliminary report is the result of a cooperative investigation on the chemical, pharmacological and chemotherapeutic properties of this substance.

Fleming noted that a mould produced a substance which inhibited the growth, in particular, of staphylococci, streptococci, gonococci, meningococci and *Corynebacterium diphtheriae,* but not of *Bacillus coli, Haemophilus influenzae, Salmonella typhi, P pyocyanea, Bacillus proteus* or *Vibrio cholerae.* He suggested its use as an inhibitor in the isolation of certain types of bacteria, especially *H influenzae.* He also noted that the injection into animals of broth containing the substance, which he called "penicillin," was no more toxic than plain broth, and he suggested that the substance might be a useful antiseptic for application to infected wounds. The mould is believed to be closely related to *Penicillium notatum.* Clutterbuck, Lovell, and Raistrick (1932) grew the mould in a medium containing inorganic salts only and isolated a pigment—chrysogenin—which had no antibacterial action. Their culture media contained penicillin but this was not isolated. Reid (1935) reported work on the inhibitory substance produced by Fleming's mould. He did not isolate it but noted some of its properties.

During the last year methods have been devised here for obtaining a considerable yield of penicillin, and for rapid assay of its inhibitory power. From the culture medium a brown powder has been obtained which is freely soluble in water. It and its solution are stable for a considerable time and though it is not a pure substance, its anti-bacterial activity is very great. Full details will, it is hoped, be published later.

[The authors then presented their work on the pharmacology and toxicity of penicillin in normal animals, the effects on bacteria *in vitro* and the therapeutic affect of penicillin in mice experimentally infected with streptococci, staphylococci, and *Clostridium septique.]*

Summarising the data given in the table we see that in the final streptococcus experiment (no. 2) whereas 25/25 controls died, 24/25 treated animals survived. With *Staphylococcus aureus* the final experiment (no. 2) shows 24/24 deaths of the controls and 21/24 survivals among the treated. Lastly, with *Cl septique* when the larger doses of penicillin were given (bottom line) the figures are 25/25 control deaths and 24/25 treatment survivals.

[The investigators then presented their conclusions.]

The results are clear cut, and show that penicillin is active *in vivo* against at least three of the organisms inhibited *in vitro.* It would seem a reasonable hope that all organisms inhibited in high dilution *in vitro* will be found to be dealt with *in vivo.* Penicillin does not appear to be related to any chemotherapeutic substance at present in use and is particularly remarkable for its activity against the anaerobic organisms associated with gas gangrene.

In 1971, Chain (who had become a Nobel Laureate in 1945) wrote an article entitled "Thirty Years of Penicillin Therapy,"[14] in which he "told it like it was":

In 1935, a few months after his appointment to the Chair of Pathology at Oxford, I was invited by Professor HW Florey, as he then was, to join his staff at the Sir William Dunn School of Pathology. ...

When Florey and I in our first meetings discussed the future possible research programme of the biochemical section in his Department which I was to organize, Florey drew my attention to a very striking lytic phenomenon in which he, himself, had been interested for some years (Goldsworthy & Florey 1930). In 1924, Alexander Fleming (Fleming 1924), a bacteriologist working at St Mary's Hospital, London had made the observation that tears, nasal secretion and egg-white contained a substance which was capable of dissolving thick suspensions of a saprophytic bacterium which Fleming had isolated from the air. The bacterium was termed by Fleming *Micrococcus lysodeicticus.* The active lytic substance had obvious enzymic properties, but the substrate on which it acted in the bacterial cell was not known, and Florey suggested to me that it would be interesting to attempt to isolate and characterize this substrate, if indeed lysozyme was an enzyme. The reason why Florey was interested in lysozyme was not so much its antibacterial power which was of a very limited range, but the fact that, in addition to the sources I have just mentioned, it also occurred in duodenal secretions, and Florey thought at that time that it might play a role in the mechanisms of natural immunity and, in particular, could be involved in the pathogenesis of duodenal ulcers.

The study of the biochemical mode of action of a powerful bacteriolytic agent, as lysozyme obviously was, was a problem exactly representative of the kind which has always attracted my particular interest. I

therefore took up Florey's suggestion with enthusiasm and started the work in 1936 with a PhD student, LA Epstein, an American Rhodes scholar. We were able to show that lysozyme was an enzyme of polysaccharidase nature acting on a polysaccharide which we could isolate from dried bacterial cells of *M lysodeicticus.*

[Chain then recounts his literature survey of bacteriolytic agents which led him to observations on inhibition of growth of one bacterial species by another (without actual lysis), to the phenomenon of microbial antagonism, and to Fleming's work on *Penicillium notatum.]*

I should like to point out that the possibility that penicillin could have practical use in clinical medicine did not enter our minds when we started our work on penicillin. A substance of the degree of instability which penicillin seemed to possess according to the published facts does not hold out much promise for practical application. If my working hypothesis had been correct and penicillin had been a protein, its practical use as a chemotherapeutic agent would have been out of the question because of anaphylactic phenomena which inevitably would have followed its repeated use. From the scientific point of view, however, the problem of purifying penicillin and isolating the substrate on which I thought it acted was of interest and hence well worth pursuing.

I started to work on penicillin in 1938, long before the outbreak of the war. The frequently repeated statement that the work was started as a contribution to the war effort, to find a chemotherapeutic agent suitable for the treatment of infected war wounds, has no basis. The only reason which motivated me to start the work on penicillin was scientific interest. I very much doubt, in fact, whether I would have been allowed to study this problem at that time in one of the so-called "mission oriented" practically minded industrial laboratories. The research on penicillin, which was started as a problem of purely scientific interest but had consequences of very great practical importance, is a good example of how difficult it is to demarcate sharp limits between pure and applied research.

One wonders why some of the substance of these last two paragraphs was not included in the 1940 report instead of the less informative "following the work on lysozyme in this laboratory it occurred to two of us that it would be profitable to conduct a systematic investigation of the chemical and biological properties of the antibacterial substances produced by bacteria and moulds." Perhaps the original manuscript "told it like it was" and the editor of the journal cut it out.

Conclusions

We all are "frauds" at one time or another. In 1945, Robert Dripps and I tried whenever possible in our laboratory course in pharmacology to demonstrate the action of drugs in unanesthetized man instead of in anesthetized cats or dogs or pithed frogs. That year, we decided to demonstrate on man the highly specific neuromuscular block produced by tubocurarine. We realized that the safest way was to produce a local block, ie, to give tubocurarine intra-arterially, preferably into the brachial artery, while the corresponding arm veins were occluded. We asked for a volunteer and gave him a very small dose of d-tubocurarine intra-arterially. To our astonishment, huge wheals and flares soon covered much of his forearm. We immediately thought that our subject was sensitive to curare preparations. Another student volunteered and we repeated the experiment and got the same result. Now we decided to skin test the third volunteer; intracutaneous injection produced a wheal and flare similar to that following histamine. At this point, a student said, "How about skin-testing all of us?" We did—and all 13 soon had characteristic histamine-like wheals. That's how we discovered that tubocurarine liberated histamine from the skin of man.

But that's not how we wrote our report![15] We wrote a typical IMRAD article that gave no indication of why or how we did the study. I'm sure we never considered any other format in 1945; we simply conformed to the pattern.

There's little doubt that most scientists advocate impersonal, cold, unrevealing scientific writing, devoid of human interest or even of speculation. Lord Brain, in a reply to Medawar's use of the word "fraud,"[3] said, "... it does not seem to me to follow that the structure of the scientific paper, the object of which is to communicate something to the reader, should necessarily correspond to the logical process by which the discovery was made."[16] Lord Brain is correct if all that scientists want to know are the methods, data, and conclusions. Medawar is correct if it's important to science to learn how discoveries have come about. Maybe we can have both. Let scientists use their IMRAD manuscripts to tell how they would have done their experiments if they had proceeded with impeccable logic from the first experiment to the last; this will be comforting to their ego. But let them send with the manuscript a sealed enve-

lope that contains an account that "tells it like it was"— the envelope to be opened upon the author's death or award of the Nobel prize, when the ego no longer needs comforting.

JULIUS H. COMROE, JR.

References

1. Comroe JH Jr. Retrospectroscope: pulmonary diffusing capacity for carbon monoxide. Am Rev Respir Dis 1975;111:225-228.
2. Schilling HK. A human enterprise. Science as lived by its practitioners bears but little resemblance to science as described in print. Science 1958;127:1324-1327.
3. Medawar PB. Is the scientific paper fraudulent? Yes; it misrepresents scientific thought. Sat Rev Aug 1, 1964, pp 42-43.
4. Comroe JH Jr. Retrospectroscope: the inside story. Am Rev Respir Dis 1976;113:381-385.
5. Ringer S. A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart. J Physiol (Lond) 1883; 4:29-42.
6. Chargaff E, Olson KB. Studies on the chemistry of blood coagulation. J Biol Chem 1937;122:153-167.
7. McLean J. The thromboplastic action of cephalin. Am J Physiol 1916;41:250-257.
8. McLean J. The discovery of heparin. Circulation 1959;19:75-78.
9. Hustin A. Principe d'une nouvelle methode de transfusion muqueuse. J Med Bruxelles 1914;12:436-439. (For "muqueuse" read "sanguine.")
10. Hustin A. Renouveau de la transfusion sanguine au début du XX siècle. Acta Chir Belg 1960;8:762-780.
11. Jacobson JH, Suarez EL. Microsurgery in anastomoses of small vessels. Surg Forum 1960;11:243-245.
12. Macmillan WH, Smith DJ, Jacobson JH. Response of normal, denervated, and reserpine-treated arteries to sympathomimetic amines and nicotine in dogs. Br J Pharmacol Chemother 1962;18:39-48.
13. Chain E, Florey HW, Gardner AD, Heatley NG, Jennings MA, Orr-Ewing J, Sanders AG. Penicillin as a chemotherapeutic agent. Lancet 1940;2:226-228.
14. Chain E. Thirty years of penicillin therapy. Proc R Soc Lond [Biol] 1971;179:293-319.
15. Comroe JH Jr, Dripps RD. The histamine-like action of curare and tubocurarine injected intracutaneously and intra-arterially in man. Anesthesiology 1946; 7:260-262.
16. Brain WR. Structure of the scientific paper. Br Med J 1965;2:868-869.

Nocturnal Asthma Mechanisms and Treatment, edited by Richard J Martin MD. Hardcover, 394 pages, illustrated. Mount Kisco NY: Futura Publishing Co, 1993. $72.00.

Asthma is an important clinical problem that has been documented to be increasing in prevalence and severity in the United States, with a 29% increase in prevalence between 1980 and1987, a threefold increase in hospitalizations between 1970 and 1987, and a 31% increase in mortality from 1980 to 1987.[1] These increases prompted the National Heart, Lung & Blood Institute (NHLBI) to constitute an expert panel to study the problem and issue a consensus recommendation on the diagnosis and management of asthma, in 1991.[1]

Nocturnal asthma, the exacerbation of asthma or worsening of asthmatic symptoms in the early morning hours, has long been recognized as a problem affecting a large percentage of asthmatic patients. The purpose of this book is to provide an in-depth view of this specific aspect of the physiology and treatment of bronchial asthma. It is of interest that the 1991 monograph on asthma,[1] which does include many special problems and situations (such as occupational asthma, treatment of asthma during pregnancy, and the asthmatic patient undergoing surgery), does not have a section on nocturnal asthma.

In this volume, 11 contributors have joined to write 10 chapters covering this topic. The first two chapters deal with *chronobiology*. They describe how natural biologic rhythms play a role in many disease states, including asthma. For instance, surgical death rates peak at 1:00 AM. Live spontaneous births and asthma crises peak at 4 AM. An understanding of these rhythms may provide important information for treatment. A single chapter gives an overview of nocturnal asthma as a problem. Another chapter deals specifically with the interaction of sleep and asthma. Two chapters discuss the effect of cell-mediated immune factors on nocturnal asthma, and the last four chapters cover the treatment of nocturnal asthma.

Overall, the book is well written. and the topic is well covered. Figures are large, to the point, and easy to interpret, although mostly obtained from other previously published sources.

In many ways, understanding the physiology and treatment of nocturnal asthma will help the practitioner understand the pathophysiology of asthma in total. Nevertheless, the narrow scope of this book will attract only a limited audience. It should certainly not be the lone reference on asthma in any practitioner's library. With the availability of other, more comprehensive books on asthma, most practitioners will not feel the need to include this book in their libraries. It is more likely to be purchased by libraries and those individuals with either special interest in asthma (or specifically nocturnal asthma) or by those desiring rather extensive book collections.

Philip Schiffman MD
Clinical Associate Professor
of Medicine
Division of Pulmonary &
Critical Care Medicine
University of Medicine & Dentistry
of New Jersey
Robert Wood Johnson
Medical School
New Brunswick, New Jersey

REFERENCE

1. National Asthma Education Program. Guidelines for the diagnosis and management of asthma: expert panel report. Bethesda MD: National Heart, Lung and Blood Institute, 1991. (NIH publication no. 91-3042.)

Drugs and the Lung, edited by Clive P Page PhD and W James Metzger MD, with 33 contributors. Hardcover, 607 pages, illustrated. New York: Raven Press, 1994. $126.00.

This is the first of a proposed series of monographs entitled Advances in Clinical Pharmacology, edited by Nobel Laureate Sir John Vane. Of the 33 contributing authors, 15 are from the United States, 13 from the United Kingdom, 2 from Italy, and 1 each from Sweden, Finland, and Australia. The book is divided into two sections, the first dealing with drugs in current clinical use and the second with drugs and therapeutic approaches that are novel or experimental.

The first section contains 9 chapters; the first 7 are devoted to drugs used in the treatment of asthma. All 7 of these reviews are comprehensive and well documented. The chapter on glucocorticosteroids is especially noteworthy, detailing the uses of steroids not only in asthma but also in chronic obstructive and interstitial lung diseases, pulmonary vasculitis, adult respiratory distress syndrome (ARDS), and other conditions. There are 657 references cited. Chapter 8, by two British authors, is devoted to chemotherapeutic agents for lung cancer. Chapter 9, entitled Antibiotics and the Lung, contains only reviews of antibacterial drugs.

The second section is authored mainly by researchers reporting on new drugs. The principal emphasis is on asthma, with articles on potassium-channel openers, phosphodiesterase inhibitors, bradykinin, and antagonists to platelet activating fac-

tor and selected tachykinins. Leukotrienes are discussed in the final chapter on mechanisms of airway inflammation. A single chapter addresses the present status of drug therapy for ARDS, reviewing a broad spectrum of topics from anti-endotoxin immunotherapy to surfactant replacement; 280 references are cited.

The book is essentially a series of complete reviews of selected aspects of bronchopulmonary therapeutics. There are no discussions of mucolytic or antitussive drugs. Antimicrobial agents reviewed do not include antifungal, antiparasitic, or antiviral compounds. Tuberculosis is mentioned only in connection with glucocorticoid administration in miliary disease or tuberculous pleuritis. In the arcane terminology of pharmaceutical research, many acronyms are employed. Although this reduces text length, it requires that the reader turn back to find their meanings; tables of abbreviations would be helpful to those unfamiliar with these subjects.

This is an excellent sourcebook on drugs for asthma, for uses of corticosteroids in lung disease, and for new bronchoactive agents. It is not intended to be a textbook on pharmacology for a respiratory care curriculum. **Drugs and the Lung** will be a timesaver for the interested reader pursuing the specialized topics within its scope.

Hugh S Mathewson MD
Professor Emeritus
Anesthesiology
Professor
Respiratory Therapy Education
University of Kansas Medical Center
Kansas City, Kansas

Pulmonary Care of the Surgical Patient, edited by Leland H Hanowell MD and Forrest L Junod MD. Hardcover, 400 pages, illustrated. Mount Kisco NY: Futura, 1994. $65.00.

If the old adage is true that "an ounce of prevention is worth a pound of cure", then this is a welcome book. Despite the many recent advances in surgery, practitioners and their patients are still dogged by the same old problems that contribute significantly to morbidity and mortality even with a well-executed operation. The incidence of asthma is not decreasing; if anything, mortality from asthma is increasing. Pulmonary embolism, particularly common in the surgical population, still has a mortality rate approaching 40%. Although many studies support the routine use of preventive therapy, surprisingly few surgeons employ prophylaxis.

This book is written for anyone involved in the perioperative management of the surgical patient and should appeal to surgeons, respiratory therapists, and intensivists alike. It is a small book, comprising 11 chapters. Most chapters are written by different authors, with contributions from anesthesiologists, pulmonologists, and surgeons. It neither is nor claims to be a complete definitive textbook on the pulmonary complications of surgery. Instead, each chapter describes in an isolated fashion a specific topic—asthma, adult respiratory distress syndrome, mechanical ventilation, antibiotics, pain management, and pulmonary embolism, to list just 6 of the chapters. In this regard, it is effective as a manual or handbook with clearly delineated algorithms and tables. However, what will broaden the appeal of this book to the thinking practitioner is how it exhaustively reviews the current literature to give a well-balanced account of each mode of therapy. For example, in the chapter on pulmonary embolism, not only do the authors describe the theory behind venography, impedance plethysmography, radiofibrinogen leg scanning, and ultrasound as methods of detection for deep venous thrombosis, but also quantitate side effects, shortcomings, and sensitivity and specificity for each modality by review of recent studies. This chapter alone contains 287 references, yet it reads in a concise and clear manner. Similarly, the short chapter on mechanical ventilation, in addition to describing more traditional modes, also details extracorporeal membrane oxygenation and low-frequency positive pressure ventilation. It is a critical description, with references to outcome studies.

This is a good book. Despite its pithy nature, it will be enjoyed by anyone interested in a balanced, scientific approach based on an unbiased review of recent literature. It is not a didactic book of do's and don'ts. It is concise and readable, which makes it welcome at a time when large tomes seem to be the norm. This, along with its stout binding and good quality paper, seems to justify the price.

Philip McArdle MD
Critical Care Fellow
Department of Anesthesiology
University of Virginia
Charlottesville, Virginia

Letters on topics of current interest or commenting on material in RESPIRATORY CARE will be considered for publication. The Editors may accept or decline or edit a letter without changing the author's views. The content of letters as published may simply reflect the author's opinion or interpretation of information—not standard practice or the Journal's recommendation. Authors of criticized material will have the opportunity to reply in print. No anonymous letters will be published. Type letters double-spaced, mark "For Publication," and mail to RESPIRATORY CARE Journal, 11030 Ables Lane, Dallas TX 75229-4593.

Letters

Administration of Air When Oxygen Was Intended

I am writing this letter to voice my concern about an egregious, yet avoidable, clinical error—administration of medical air when oxygen is intended. In my institution, the respiratory care department's policy for the administration of small volume nebulizer treatments recommends that oxygen be used as the source gas except with COPD patients who have documented CO_2 retention.

Clinicians can deliver medical air to the patient using an air compressor or an air flowmeter. Air flowmeters have an oxygen outlet thread (diameter-index safety system [DISS] connection number 1240) that makes it physically possible to connect the standard small-bore connecting-tube adapter that is used with oxygen therapy appliances and to administer a gas that is not intended.[1]

Using air as a source gas poses no problem for normoxic patients; however, when oxygen therapy appliances are mistakenly connected to the air flowmeter, serious problems can ensue. Such errors may include the mistaken connection of manual resuscitation bags to the air flowmeter during cardiac and respiratory arrest. In my institution, I have observed this error in the emergency room and in other areas of the hospital, and it has been made by emergency medical technicans, nurses, and respiratory care practitioners. As might be expected, patients have consistently experienced oxygen desaturation.

My experience led me to conduct an informal survey of my peers in several Boston teaching hospitals. Without exception, the respondents agreed that their experience was similar to mine and claimed frustration with their inability to limit the inadvertent connection of oxygen therapy appliances to air flowmeters.

Egan's Fundamentals of Respiratory Therapy[1] states, "... the DISS is used, in Respiratory Care, to connect flowmeters and other therapy devices such as nebulizers, ventilators, and anesthesia apparatus, to a low pressure gas source."[1] Therefore, I propose that the diameter-index safety system standards be enforced with flowmeters. I ask that other practitioners join me in demanding that manufacturers produce flowmeters with an outlet that complies with the DISS standard and prevents the inadvertent administration of medical air. I recognize that some inconvenience and even expense will result initially, but the use of medical air and air flowmeters can be largely supplanted with the use of metered-dose inhalers and portable air compressors. It will undoubtedly take some time before the devices intended for use with air are fitted with a proper air connection—DISS connection number 1160[1]—and made available for purchase.

I expect that my recommendation will meet with some resistance from manufacturers, and perhaps even practitioners, because even positive change is difficult. However, if all we suffer are the pangs of change, and the risk to our patients is reduced as I have described, I believe we shall all applaud the effort in the end.

William R Howard MBA RRT
Director, Respiratory Care Programs
New England Medical Center
Boston, Massachusetts

REFERENCE

1. Thalken RF. Production, storage, and delivery of medical gases. In: Scanlan CL, Spearman CB, Sheldon RL, eds. Egan's fundamentals of respiratory therapy, 5th ed. St Louis: CV Mosby, 1990: 584-605.

Piedalue Wants More Answers about Airway Pressure and Pulmonary Mechanics

In the August 1993 issue of the Journal,[1] Dr David Pierson responded to my plea for some answers related to active expiration in ventilated patients. But somehow my questions weren't all answered.

I did not ask about the lungs of trumpet players. I am certain they have great lungs. Also, I can personally cough to much higher pressures. If all ventilated patients had normal homogeneous lungs, I would not have posed those questions. Dr Pierson, how can you conclude that both pressure and volume change in the same direction in all alveoli in ARDS?

Regarding resistance, it's obvious that you have problems with two statements in my letter. However, why is airway resistance (R_{aw}) reported at a standard flow of 0.5 L/s if flowrate does not affect resistance as you suggest? I would like to challenge you to do two clinical tests.

Do an easy test. First, go to any ventilated patient and calculate the airway resistance using all reasonable flows (ie, 40, 50, 60, 70, up to 120). This might look better if you get the same value for R_{aw}. But you won't!

Second, you say high flowrates can be achieved through very small orifices if the driving pressure is high enough. Why do large volume nebulizer systems only accept a flowrate of 15 L/min? The driving pressure is 50 psig, but the flow won't get any higher the more the flowmeter is opened.

In return, I will try a test in Denver (tongue-in-cheek). I will suggest that

our next ARDS patient play the trumpet—and see what happens.

Fran Piedalue BS RRT
Educational Coordinator
University Hospital
Denver, Colorado

REFERENCE

1. Piedalue F. A reader poses questions about peak airway pressure (letter), with response by DJ Pierson. Respir Care 1993;38(8):952-953.

Pierson responds:

This is a follow-up (somewhat belated) to Fran Piedalue's letter and my response published in the August issue (Respir Care 1993;38[8]:952-953), and also to her second letter, published above. My original response did not completely settle the issues of peak airway vs alveolar pressures during mechanical ventilation and the possible role of high peak *expiratory* pressures in ventilator-related barotrauma, and I was not entirely correct in my statements about flow and resistance. For a more in-depth discussion of, and a different perspective on, the physiology involved, I consulted Dr Jacob Hildebrandt, Professor of Physiology and Biophysics at the University of Washington, who is an internationally recognized authority on pulmonary mechanics. Dr Hildebrandt has explored the issue more analytically and more didactically than I did, and has kindly shared his response to Fran Piedalue's questions in the letter immediately following this one.

David J Pierson MD
Medical Director
Respiratory Care
Harborview Medical Center

Professor of Medicine
University of Washington
Seattle, Washington

Hildebrandt responds:

Piedalue's key question [Respir Care 1993;38(8):952-953] concerns the possible association in ventilated patients between pneumothorax and the resumption of coughing during recovery. This association must be uncommon but might occur in patients with elevated airflow resistance. The mechanism could be related to successive inspiratory gasps, with an inability to expel the entire added gas volume. The retained excess volumes then added to that supplied by the ventilator could result in hyperinflation. This scenario would implicate lung overdistention as the principal etiologic factor in the associated pneumothorax. But why necessarily not peak airway or alveolar pressure?

It is well understood that the inlet pressure (P_{ao}) applied to a tracheal tube is not the same as alveolar pressure (P_A) *except* when flow is zero *and* airways are open. However, the significance of P_A itself is less obvious. In fact, in order to make useful interpretations of P_A, a knowledge of the circumstances at the time of measurement is required. A high end-inspiratory pressure (ie, P_A) of, say, 75 cm H_2O, could be found in a variety of situations, such as: (1) the lungs are normal and the chest wall is relaxed but very stiff, making pleural pressure (P_{pl}) very positive (eg, +60 cm H_2O); (2) both the lungs and chest wall are again normal, but the pressure around the chest is high (eg, pressure on the chest, underwater breath-hold, scuba diving); (3) both lungs and chest wall are normal but the expiratory muscles are active (P_{pl} again +60 H_2O) as in cough or Valsalva maneuver; (4) the lungs are fairly normal but the abdomen is turgidly overdistended (effectively, like [1] above); (5) the lungs are very stiff, leaving P_{pl} quite normal (eg, +5 cm H_2O); (6) the lungs are fairly normal but a mispositioned endotracheal tube expands only one lung—but to a dangerous degree; and (7) both lungs are grossly and dangerously overdistended inside a normal chest wall.

Of the foregoing examples, only in the last three would lung distending pressure (P_L), equal to $P_A - P_{pl}$, become abnormally high, and thus present risks for pneumothorax. By contrast, in the first four examples, structures *around* the lungs serve to oppose most of the applied P_A, such that P_{pl} is made quite positive but P_A-P_{pl} is limited at a safe level. *The important point is that P_A by itself is not hazardous to lungs, but a high P_A-P_{pl} gradient is to be avoided if at all possible.*

Piedalue also raises the interesting issue of inhomogeneities, and these deserve some discussion. In general, only a large transpulmonary gradient P_A-P_{pl} can bring about overinflation of the most compliant parts of the lung, and again a high P_A per se is not of consequence. This is true whether expiratory flow is or is not occurring, as in a cough. By example (3) above, during cough the P_{pl} is elevated throughout the chest. However, although some regions may empty more slowly than others, they can never become overinflated in the process.

Nevertheless, *uneven emptying* does generate extra internal stresses including shears at the boundaries between regions. In extreme cases, we know that local atelectasis or airway plugging must give rise to extra stresses around such collapsed regions during inspiration. To what extent these 'interdependence' forces may be responsible for tissue disruption is not known, but the possibility needs to be considered. We do know that normal subjects breathing oxygen at low functional residual capacity can develop extensive atelectasis, and that subsequent deep breaths may elicit sharp pains, suggesting that local tissue tensions from this mechanism may indeed become dangerously high.

Another aspect of inhomogeneities that Piedalue raises is the possible hazard of shortening the inspiratory time by increasing inspiratory flowrates (and thus also peak applied pressure). In the presence of very uneven time constants, the branches with the shortest time constants fill first. If they are also most compliant, they may transiently become overdistended. In the most extreme cases, some regions may get no ventilation, as in example (6) above, forcing the remainder into overinflation.

Could inspiratory flowrate to a region ever be "limited" in the way that expiratory flow limitation commonly happens? Probably not, for two reasons: (1) even in turbulent conditions flowrate can increase when driving pressure is raised, and (2) bronchial transmural pressure during inflow always *distends* the airways, but always acts to narrow them on expiration.

I would also like to clarify some points in Dr Pierson's letter (Respir Care 1993;38[8]:953). He used the vague term "transalveolar" pressure instead of one of the more established physiologic terms such as transpulmonary pressure, P_{tp} (defined as $P_{ao} - P_{pl}$), or lung recoil pressure, P_L (defined as $P_A - P_{pl}$). (Although "transalveolar pressure" is currently popular with some clinicians, the latter two terms are clearer and technically more accurate.) We note that at zero flow $P_L = P_{tp}$. As emphasized above, it is P_L that is of prime importance when considering overdistension.

He also argued that flow in tubes ($\dot{V}$) was proportional to driving pressure, which would be true only for lower (Poiseuille) flowrates; at higher flowrates at which turbulence occurs, the driving pressure becomes proportional to $\dot{V}^2$. Accordingly, R_{aw} must be measured at some standard low flowrate, such as 0.5 L/s. At higher $\dot{V}$, the measured R_{aw} would increase. At maximum expiratory flow, which develops in compliant tubes or airways, the flow limitation phenomenon is seen, wherein $\dot{V}$ remains constant even when driving pressure is raised. In this range, R_{aw} must vary directly with driving pressure ($R_{aw} = [P_A - P_{ao}]/\dot{V}$, and $\dot{V}$ = constant). Finally, flow can become limited even in rigid tubes, but this requires sonic gas velocities and never occurs in physiologic systems (but could occur at a wall outlet driven by, eg, 50 psi, or about 3,400 cm H_2O).

Finally, with respect to optimizing ventilator settings, alarms, and peak pressure limits, it is clear that no hard and fast universal rules can be established to suit all situations. However, if we can understand and agree on the principles governing the mechanical behavior of the respiratory system that apply even in complex pathologic states, then—and only then—do we all stand in a better position to make better decisions, do less harm, and usually do more good. Thank you, Fran, for challenging us.

Jacob Hildebrandt PhD
Professor of Physiology &
Biophysics
Professor of Medicine
University of Washington
Health Sciences Center
Seattle, Washington

An Addition to "Flow-Triggering Systems"

I read with interest Branson's description of flow-triggered ventilators, in the recent Kittredge's Corner.[1] Present-day flow-triggering has been developed by the diligent efforts of many, including the Swedish engineers who developed the Engstrom ERICA (mistakenly identified by Branson as the EDITH, ahygroscopic condenser humidifier, or HCH).

The ERICA (an acronym for Engstrom respirator for intensive care application), which arrived in the U.S. marketplace about 1981, was flow triggered and time cycled—characteristics not shared by its competitors. The ventilator also incorporated extended mandatory minute ventilation (EMMV), inspiratory assist (ie, pressure support), and an impressive list of monitoring capabilities (including airway resistance, compliance, end-tidal CO_2, and V_D/V_T)—impressive for the time by anyone's standards.

Ray Monast RRT
Clinical Operations Manager
Windward Health Care
Marlborough, Massachusetts

REFERENCE

1. Branson RD. Flow-triggering systems (Kittredge's Corner). Respir Care 1994;39(2):138-144.

Mr Branson responds:

I appreciate Mr Monast's comments on the latest Kittredge's Corner. He is, of course, correct in recognizing that the Engstrom ventilator is the ERICA and that the EDITH is the Engstrom artificial nose.

Engstrom often fails to receive credit for introducing the concept of flow triggering. However, the flow-triggering system used by Engstrom was different from those we described. In the ERICA, the expiratory valve remained closed until the patient's inspiratory effort created a flow of 0.1 L/s. Flow was measured by a fixed-orifice flow transducer, which Engstrom called "the Venturi tube." This means that the patient's initial inspiratory effort was against a

closed system until flow exceeded 0.1 L/s (6 L/min).

I have no frame of reference for comparing the work of breathing on the ERICA to the flow-triggering systems now in use, and I am unaware of any data. I could speculate that the initial effort may have caused some patient discomfort. In any event, Engstrom did, in fact, develop the first flow-triggering system.

Richard D Branson RRT
Assistant Professor
Department of Surgery
University of Cincinnati Medical Center
Cincinnati, Ohio

1994 Summer Forum

Join us (along with other respiratory care managers and program directors) in St Petersburg for a comprehensive educational experience that will help you navigate your way through the challenging health care environment.

We offer the most current information on today's complex issues.

For more information contact AARC
11030 Ables Lane
Dallas, TX 75229
(214) 243-2272

The 1994 Summer Forum is approved by the American Association for Respiratory Care for up to 15 hours of CRCE credit.

Neonatal Respiratory Care IISP

Recognition and Stabilization of the Premature Infant in Respiratory Distress
This IISP helps you identify primary risk factors associated with premature birth. Discusses and explains the importance of providing a neutral-thermal environment for the premature infant and the necessity for continuous non-invasive oxygen monitoring of the premature infant in supplemental oxygen. You will also learn to recognize aberrant blood gases in the neonate and oxygen therapy initiation with an oxygen hood.
Item NN1 $10 Ea.
Add $3 for shipping and handling.

Also Available
Theory and Application of Neonatal Ventilation
By Robert Chatburn, RRT. Knob-turning in the neonatal intensive care unit should be a profound activity because it often has profound consequences. Presents a well-organized and systemic approach for managing mechanical ventilation. Discusses the multiple effects of ventilator adjustment and how consideration of controls are interrelated with optimum care. (60 minutes VHS)
Item VT25 $40 Ea. (Members $35).
Add $3 for shipping and handling.

To Order Call (214) 243-2272
or Fax to (214) 484-2720
Purchase Order · MasterCard · Visa

American Association for Respiratory Care
11030 Ables Lane, Dallas, TX 75229-4593

How You Can Help Patients Stop Smoking:

Opportunities for Respiratory Care Practitioners

The National Heart, Lung, and Blood Institute has made available "How You Can Help Patients Stop Smoking: Opportunities for Respiratory Care Practitioners." This guide was developed in collaboration with the AARC and provides guidance on talking to patients about smoking. Plus, it tells you how to integrate a smoking intervention program into a respiratory care department. Includes strategies for community outreach and information on smoking intervention techniques and tools.
Single copies are free of charge by calling or writing:

The National Heart, Lung, and Blood Institute
Education Programs Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
(301) 951-3260

YOURS FREE!

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Form Approved: OMB No. 0910-0291 Expires: 12/31/94
See OMB statement on reverse

FDA Use Only (RESP CARE)

Triage unit sequence #

Page ____ of ____

A. Patient information

1. Patient identifier
In confidence

2. Age at time of event:
or
Date of birth:

3. Sex
☐ female
☐ male

4. Weight
____ lbs
or
____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____ (mo/day/yr)
☐ life-threatening
☐ hospitalization – initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other: ____

3. Date of event (mo/day/yr)

4. Date of this report (mo/day/yr)

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1
#2

2. Dose, frequency & route used
#1
#2

3. Therapy dates (if unknown, give duration)
from/to (or best estimate)
#1
#2

4. Diagnosis for use (indication)
#1
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
– –

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
☐ health professional
☐ lay user/patient
☐ other: ____

5. Expiration date (mo/day/yr)

6.
model # ____
catalog # ____
serial # ____
lot # ____
other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

2. Health professional?
☐ yes ☐ no

3. Occupation

4. Also reported to
☐ manufacturer
☐ user facility
☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

FDA Form 3500 (6/93)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

- 1-800-FDA-0178 to FAX report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 for more information or to report quality problems
- 1-800-822-7967 for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send your comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building,
Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
ATTN: PRA

and to:
Office of Management and Budget
Paperwork Reduction Project
(0910-0230)
Washington, DC 20503

Please do NOT return this form to either of these addresses.

FDA Form 3500-back

Please Use Address Provided Below – Just Fold In Thirds, Tape and Mail

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES OR APO/FPO

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE, MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH
The FDA Medical Products Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

Not-for-profit organizations are offered a free advertisement of up to eight lines to appear, on a space-available basis, in Calendar of Events in RESPIRATORY CARE. Ads for other meetings are priced at $5.50 per line and require an insertion order. Deadline is the 20th of the month two months preceding the month in which you wish the ad to run. Submit copy and insertion orders to Calendar of Events, RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593.

Calendar of Events

AARC & AFFILIATES

June 8-10 in Round Top, New York. The Seventh Annual Managers/Educators Rocking Chair Conference at the Winter Clove Inn and Conference Center is sponsored by the NJSRC, NYSSRC, AARC, and Allied Health Care Services of Orange NJ. The conference, offered to all respiratory managers, supervisors, and educators, features Sherry Milligan, Associate Executive Director of the AARC, and Carl Wiezalis of SUNY Health Science Center. Topics include national healthcare reform and its impact on healthcare delivery, marketing the RCP, preparing for on-site inspections from JRCRTE and JCAHO, and protocols. The registration fee is $225, which includes conference registration, lodging for two nights, meals, and gratuities. The same package with one night's lodging is $175. Contact Ken Wyka at (201) 982-7228 or Joseph Sorbello at (315) 464-6872.

June 8-10 in Checotah, Oklahoma. The OSRC presents its 29th Annual State Seminar and Exhibition at Fountainhead Resort and Convention Center on Lake Eufaula. This year's theme, "The Times—They Are A' Changin'," addresses anticipated changes in the healthcare delivery system and critical issues for respiratory care. Other activities include a Manager's Mixer and the traditional golf tournament. For information on the seminar or exhibits, contact Karen Hart RRT at (405) 273-6442.

June 15-17 in St Charles, Illinois. The ISRC presents its 26th annual state convention at Pheasant Run Resort. This year's theme is "ISRC Game Plan: Team Spirit '94" and features Sam Giordano MBA RRT, Executive Director of the AARC, as the keynote speaker. Mr Giordano speaks on "Health Care Reform and the RCP." New this year are breakfast sessions with choices of four topics: "CLIA Update," "OSHA Update," "Hospital-Based Nicotine Intervention Program," and "Reimbursement Issues for Home Medical Equipment Suppliers." The convention includes many other educational topics, an entry level review, and a resort setting for your enjoyment and relaxation. Contact Douglas McQueary (312) 962-4060 or Jane Reynolds (312) 883-6535.

July 6 in Corpus Christi, Texas. The TSRC will hold its 24th Annual Convention entitled "Sailing the Seas of Change." Included are forums on management, education, and research, a neonatal resuscitation certification program, and symposiums on "Clinical Data Collection" and "Respiratory Care Restructuring in Response to Health Care Reform." Patrick Dunne presents the Keynote Address. Up to 20 CRCE credits are available for the three full days. Also planned are a golf tournament, a beach party, Sputum Bowl, and evening dances. Contact the TSRC Executive Office (214) 680-2455.

July 15-17 in St Petersburg, Florida. The AARC's Summer Forum, featuring education and management programs, is held at the Don Cesar Beach Resort in St Petersburg. For details refer to the special Summer Forum Program in the April *AARC Times* or call (214) 243-2272 or fax (214) 243-2720.

July 26 AARC Videoconference. The AARC, in conjunction with VHA Satellite Network, presents the fourth of a 6-part videoconference series "Professor's Rounds in Respiratory Care." This presentation is entitled "Arterial Blood Gas Troubleshooting: Interpretation, Analysis, and Quality Control" (1 CRCE credit). For information call (214) 830-0061.

August 3-5 in Orange Beach, Alabama. The Alabama, Louisiana, and Mississippi Societies for Respiratory Care introduce their 23rd Annual Meeting of the TriState Respiratory Care Conference to be held at the Perdido Beach Resort. Presentations include "Care of Surgical ARDS"; "The Impact of Health Care Reform on Respiratory Therapists and How to Deal With It"; "Professionalism: Excellence in Presentations and Media Skills"; and "New Advances in Ventilator Technology." Participants can earn up to 10 CRCE credit hours. Call Perdido Beach Resort at (800) 634-8001 for reservations, or call (205) 981-9811 in Alabama. Hotel reservations must be received by July 2. Contact Rocco Tretola BS CRTT, TriState Respiratory Care Conference, 6558 Orleans Ave, New Orleans LA 70124. (504) 482-3530.

August 17-19 in Atlantic Beach, North Carolina. The NCSRC hosts its 16th Annual Symposium, "Clinical Technology: Accessing Our Future," at the Sheraton Resort. Contact Beverly Dukes (704) 342-6795 or Debby Harlan (704) 379-5889.

September 13 AARC Videoconference. The AARC, in conjunction with VHA Satellite Network, presents the fifth of a 6-part videoconference series titled "Professor's Rounds in Respiratory Care." The fifth presentation is entitled "Hospital Operational Restructuring and Respiratory Care" (1 CRCE credit). For information call (214) 830-0061.

September 22-23 in Napa, California. Chapter 10 of the CSRC, the American Lung Association of the Redwood Empire, and the Respiratory Therapy Program at Napa Valley College present the 12th Annual Napa Valley Conference, "Current Concepts in Cardiopulmonary Care." Topics include synchronized ventilation in neonates, endoscopic thoracic surgery for pulmonary patients, noninvasive ventilation in the acute care setting, waveform analysis, home care ventilation, gammaglobulin infusion for steroid-dependent asthma, medical

chronobiology, and therapist-driven protocols. Contact Kate Benscoter at (707) 253-3145.

Sept 29-Oct 2 in London, Ontario, Canada. The Respiratory Therapy Society of Ontario (RTSO) presents its 22nd Annual Education Forum at the Radisson Hotel. Contact the RTSO Head Office, 122 Cumberland St, Suite 200, Toronto, Ontario, Canada M5R 1A6. (800) 267-2687.

OTHER MEETINGS

June 8-10 in Beaumont, Texas. St Elizabeth Hospital sponsors its 5th Annual Camp Huff-n-Puff, an asthma camp designed for children ages 7-14. The theme is "Asthma, Self Management." Classes are taught by registered respiratory therapists, with physicians as guest speakers. Fun activities are included. The camp is held at the East Texas Christian Center in Lumberton, Texas. Contact Kim Clanahan, Camp Coordinator, RC Dept, St Elizabeth Hospital (409) 899-7065.

June 10-12 in Memphis, Tennessee. St Joseph Hospital and Health Centers presents its 14th Annual Respiratory Care Symposium, a program designed to prepare candidates for the CRTT exam. Contact Konnye Warren or Dot Younginer, St Joseph Hospital, 220 Overton, Memphis TN 38105. (901) 577-2780.

June 21 in Atlanta, Georgia. The Department of Cardiopulmonary Care Sciences at Georgia State University (GSU) features Louise Nett RN RRT in a one-day workshop entitled "How to Help the Patient Stop Smoking: A Role for the Health Professional." Topics include "Who smokes and why"; "Motivating Smokers to Quit"; "Evaluating and Treating Nicotine Dependency"; and "Preventing Relapse." Contact Lynda Thomas-Goodfellow MBA RRT (404) 651-1498, or write to the Department of Cardiopulmonary Care Sciences at GSU, University Plaza, Atlanta GA 30303-3083.

August 31-September 3 in Christchurch, New Zealand. The Third Congress of the Asia Pacific Association for Respiratory Care presents "Breathing into 2001," at the Christchurch Town Hall, Christchurch, New Zealand. Contact Stephanie K Humphries, The Planit Group Limited, Event Organizers, 201 Cambridge Terrace, Christchurch, New Zealand. (643) 366-5955, fax (643) 366-5944.

March 12-15, 1995 in Denver, Colorado. The AARC and the National Jewish Center for Immunology and Respiratory Medicine announce the 5th International Conference on Pulmonary Rehabilitation and Home Ventilation at the Hyatt Regency Hotel. Postgraduate workshops on pulmonary rehabilitation, home ventilator care, sleep disorders, smoking cessation, and transtracheal oxygen are offered before and after the conference. The deadline for receipt of abstracts for poster/oral presentations on original research and clinical observations is November 1, 1994. Contact the National Jewish Office of Professional Education at (303) 398-1000.

Neonatal Respiratory Care IISP

Recognition and Stabilization of the Premature Infant in Respiratory Distress

This IISP helps you identify primary risk factors associated with premature birth. It discusses and explains the importance of providing a neutral-thermal environment for the premature infant and the necessity for continuous non-invasive oxygen monitoring of the premature infant in supplemental oxygen. You will also learn to recognize aberrant blood gases in the neonate and oxygen therapy initiation with an oxygen hood.

Item NN1 $10 Ea. Add $3 for shipping and handling

Also Available

Theory and Application of Neonatal Ventilation

By Robert Chatburn, RRT.

Knob-turning in the neonatal intensive care unit should be a profound activity because it often has profound consequences. This IISP presents a well-organized and systemic approach for managing mechanical ventilation. It discusses the multiple effects of ventilator adjustment and how consideration of controls are interrelated with optimum care.

Item VT25 $40 Ea. (Members $35). Add $3 for shipping and handling. (60 minutes VHS)

To Order Call (214) 243-2272 or Fax to (214) 484-2720 (Purchase Order · MasterCard · Visa)

American Association for Respiratory Care, 11030 Ables Lane, Dallas, TX 75229-4593

Texas customers only, please add 8¼% sales tax (including shipping charges). Texas customers that are exempt from sales tax must attach an exemption certificate.

The American Respiratory Care Foundation Awards for 1994

Allen & Hanbury Literary Awards

$2,000 for the best original paper (study, evaluation, or case report) accepted for publication from December 1993 through October 1994. This award is not limited to papers based on OPEN FORUM presentations.

Four awards of $1,000 each for papers accepted for publication from November 1993 through October 1994 based on any OPEN FORUM presentation (not limited to 1993 OPEN FORUM).

Five awards of $500 each for the best papers submitted (not necessarily published) by 1994 OPEN FORUM participants who have 'never published' in the Journal. The never-published first author must present the abstract at the Annual Meeting and must submit a paper based on the abstract before the 1994 Annual Meeting (received in the Editorial Office by November 1, 1994). Co-authors may have previously published in RESPIRATORY CARE.

Dr Allen DeVilbiss Literary Award

$2,000 cash plus travel expenses to the AARC Annual Meeting to receive the award—for the best paper published from November 1993 through October 1994 that addresses new technology or a new application of current technology in respiratory care.

Radiometer America Literary Awards

Three awards of $333 each are to be awarded to the authors of the three best features from Test Your Radiologic Skill, Blood Gas Corner, Kittredge's Corner, and PFT Corner accepted for publication from November 1993 through October 1994. All three (or none) of the features may be chosen from a specific category (eg, all three may be chosen from Blood Gas Corner).

Annual Meeting Registration Reimbursement

As in the past, any 1994 OPEN FORUM presenter (or co-author designee) will receive complimentary registration for an adequately prepared paper based on his 1994 OPEN FORUM abstract, submitted prior to or at the 1994 Annual Meeting. (If submitted on-site and accepted for review, convention registration will be reimbursed.)

All awards will be made at the 1994 Annual Meeting. Papers are judged automatically. No application is necessary.

THE NATIONAL BOARD FOR RESPIRATORY CARE—1994 Examination and Fee Schedule

	Examination Date	Application Deadline
CRTT:	July 16	May 1
	November 12	September 1
RRT:	June 4	February 1
	December 3	August 1
CPFT:	June 4	April 1
RPFT:	December 3	September 1

Fee Schedule

Entry Level CRTT—new applicant:	$190.00
Entry Level CRTT—reapplicant:	$160.00
RRT Written and Clinical Simulation—new applicant:	$190.00
Written Registry Only—new applicant:	$ 90.00
Written Registry Only—reapplicant:	$ 60.00
Clinical Simulation Only—new & reapplicant	$100.00
Entry Level CPFT—new applicant:	$100.00
Entry Level CPFT—reapplicant:	$ 80.00
Advanced RPFT—new applicant:	$150.00
Advanced RPFT—reapplicant:	$130.00

	Active	Inactive
CRTT Recredentialing:	$25.00	$ 60.00
RRT Recredentialing:		
Written Registry Examination	$25.00	$ 60.00
Clinical Simulation Examination	$65.00	$100.00
CPFT Recredentialing:	$25.00	$ 80.00
RPFT Recredentialing:	$25.00	$130.00
P/P Specialty Credentialing:	$25.00	$130.00
Membership Renewal:		
CRTT/RRT/CPFT/RPFT		$ 12.00

8310 Neiman Road • Lenexa, Kansas 66214 • (913) 599-4200

IISPs...

Individual Independent Study Packages Assist Practitioners In Expanding Their Respiratory Care Knowledge

Neonatal

Recognition and Stabllization of the Premature Infant in Respiratory Distress

New This IISP helps you identify primary risk factors associated with premature birth. Discusses and explains the importance of providing a neutral-thermal environment for the premature infant and the necessity of continuous noninvasive oxygen monitoring of the premature infant on supplemental oxygen. You will also learn to recognize aberrant blood gases in the neonate and oxygen therapy initiation with an oxygen hood.

Item NN1 $10 each

Clinical Science

Updated! Transpulmonary Pressure Changes in Breathing

Discusses the pulmonary pressures and how they vary during normal breathing and in special situations. Instructs on barometric, alveolar, intrapleural, transpulmonary, chest wall, and transthoracic pulmonary pressures.

Item CS5 $10 each

Updated! Lung Mechanics

Assists you in understanding the pulmonary characteristics of compliance and resistance, how these characteristics can change, and their influence on mechanical ventilator performance.

Item CS6 $10 each

Updated! Practical Application of Gas Laws

A common-sense approach to the gas laws and how to apply them to respiratory care. Defines the laws of Boyle, Charles, Gay-Lussac, Dalton, Graham, and Henry.

Item CS7 $10 each

Tonicity of Solutions and the Respiratory Tract

Gives you an understanding of how to predict the effects of therapeutic solutions on the respiratory tract and how to utilize them in the treatment of various respiratory tract pathologies.

Item CS8 $6 each

Updated! Carbon Monoxide Inhalation: Introduction to Physiologic Effects and Respiratory Management

Explains the effects of carbon monoxide inhalation on oxygen transport mechanisms in the body and the use of CO in physiologic tests of pulmonary function. Also covers recognition signs and symptoms, treatment of CO poisoning, and the equipment used to administer therapy.

Item CS9 $10 each

Electrical Safety in Respiratory Therapy I: Basic Electrical Circuitry

Enables you to relate the basic principles of electrical theory to commonly used equipment and procedures in the clinical environment and provides you with an understanding of electrical safery in respiratory care.

Item CS12 $6 each

Electrical Safety in Respiratory Therapy II: Identification of Electrical Hazards

Helps you identify and, where possible, minimize or eliminate common electrical hazards. Teaches differentiation between electrical hazards and which patients and hospital personnel are exposed.

Item CS13 $6 each

Bronchodilators I: Sympathomimetic Amines

Understand the results of stimulating the autonomic nervous system and the use of sympathomimetic drugs to accomplish bronchodilation. Exposes you to basic aspects of adrenergic bronchodilators and the patient situations for which they are indicated.

Item CS14 $10 each

Updated! Bronchodilators II: Anti-Cholinergics and Xanthines

Identifies the three categories of drugs which promote bronchodilation and the mechanism of action for each. This package also provides examples of drugs in each category. Clinical situations are presented with methods of bronchodilaton and rationale for methodsselected.

Item CS15 $10 each

Calculation and Preparation of Respiratory Medications

Teaches you how to calculate and prepare percentage solutions, ration solutions, solutions prepared from solutes less than 100 percent in strength, and how to prepare dosages from powdered drugs.

Item CS16 $10 each

Microbiology for Respiratory Therapy: A Review of Microbial Growth and Cross-Contamination

Provides an overview of microbiology in respiratory care, including groups and characteristics of microbes, requirements for microbial growth, cross-contamination, and prevention of transmission.

Item CS17 $9 each

Classification of Mechanical Ventilators I

Outlines the basic concepts of ventilator classification and a mathematical model of the respiratory system that provides the basis for classifying ventilator control systems. Also teaches the specific criteria for determining whether a ventilator primarily controls pressure, volume, or flow.

Item CS18 $10 each

Classification of Mechanical Ventilators II

You will learn detailed information about the control of ventilation in terms of switching from inspiration to expiration. You will also be introduced to the common drive mechanisms used in various mechanical devices.

Item CS19 $10 each

Classification of Mechanical Ventilators III

Explores the output waveforms that ventilators produce and their clinical implications. Instructs in the various modes of ventilation in terms of the specific combinations of control characteristics along with ventilator performance testing and the practical application of ventilator classification.

Item CS20 $10 each

Ventilation/Perfusion Relationships in Health and Disease

Covers the different degrees of hypoxia commonly encountered in

Choose any of the 33 IISPs, or order the entire set and

Save 10%

off the individual prices.
Item CP10 $261.90

To order, contact: AARC, 11030 Ables Ln., Dallas, TX 75229-4593, (214) 243-2272, Fax (214) 484-2720

patients with pulmonary disease. Focuses on ventilation/perfusion abnormalities, which account for much of the severe hypoxia in COPD, with alveolar hypoventilation also a contributing factor.

Item CS21 $10 each

Patient Evaluation

Pulmonary Function Assessment I: Basic Screening Studies

Understand simple spirometry results, the definition of obstructive and restrictive pulmonary disorders, and the basic pathology involved in each. Covers the four reasons for simple spirometry tests, the common parameters of lung function, and the results that are indicative of obstructive and restrictive pulmonary disorders.

Item PE3 $8 each

Pulmonary Function Assessment II: Bedside Studies

Familiarizes you with the use and interpretation of bedside pulmonary function tests. Learn how pulmonary function test results are used to assess ventilatory ability and which tests are commonly used. Also, learn the measuring instrument required for each test, how it is performed, and what is significant about the results.

Item PE4 $7 each

Pulmonary Function Assessment III: Lung Volume Determination and Closing Volume Studies

Assists in the recall of the eight subdivisions of total lung volume and their individual characteristics in health and disease. Discusses the measurement of lung volume by nitrogen washout, helium dilution, and closing volume techniques.

Item PE5 $6 each

Body Plethysmography

Explains the theory of body plethysmography and its use in the measurement of FRC and airway resistance. Defines and describes Boyle's Law, thoracic volume, airway resistance and its normal values, and the measurement of airway resistance.

Item PE6 $9 each

Sources of Error in the Determination of Blood Gas Values and pH

Familiarizes you with the errors that may occur in the analysis of blood gases and pH. These are often the most important laboratory data used in the diagnosis and treatment of pulmonary disease, and errors in these values can result in deleterious effects on patient care.

Item PE7 $10 each

Temperature Adjustment of Blood Gases and pH

Teaches you the effects of abnormal body temperature on blood gas and pH values. Blood gas values and pH are determined at 37 degrees Celsius, and this package teaches you how to adjust these values.

Item PE8 $10 each

Measurement of Static Compliances and Dynamic Characteristics Curves During Mechanical Ventilation

Learn how to compute and record static compliance curves and dynamic characteristics. And learn the procedure of obtaining pressure-volume measurements and interpret the compliance characteristics measurements.

Item PE9 $7 each

Updated! Arterial Blood Gas Interpretation

Teaches you ABG interpretation in order that the prescribed therapy can be administered in a knowledgeable manner. Describes a systematic method that allows you to correctly classify the acid/base dysfunction and to relate the diagnosis concisely and coherently.

Item PE10 $10 each

Clinical Practice

Chest Tubes and Pleural Drainage

Helps you understand the purpose of pleural drainage, how it might affect the patient's respiratory status, and what precautions you must take when working with patients who are receiving pleural drainage.

Item CP3 $10 each

Tracheal Intubation I: Upper Airway Anatomy and Goals of Intubation

After completing this IISP, you will understand the rationale for tracheal intubation and be able to identify the important landmarks of upper airway anatomy.

Item CP4 $6 each

Tracheal Intubation II: Routes of Intubation

Describes the four routes of tracheal intubation and some advantages and hazards of each. Also presents the process for selecting the most suitable route in a given situation.

Item CP5 $6 each

Tracheal Intubation III: Equipment Procedures for Intubation

Covers the selection of the proper equipment necessary to perform endotracheal intubation and to ensure that they are in working order.

Item CP6 $8 each

Respiratory Management of Neuromuscular Crisis

Teaches respiratory management of patients with ventilatory failure caused by a neuromuscular disorder. Provides a basic understanding of how neuromuscular conditions lead to ventilatory insufficiency and the considerations to be taken when working with these patients.

Item CP7 $7 each

Respiratory Management of Flail Chest

This study package helps you increase your understanding of the pathophysiology of flail chest and the respiratory management of patients who have sustained chest wall trauma that results in a flail chest.

Item CP8 $10 each

Updated! Respiratory Management of Head Trauma

Teaches identification of the five physical signs indicative of head trauma and explains the development of respiratory failure secondary to trauma. Also discusses airway management, drug therapy, ventilator parameters, acid-base status, and measures to be taken to maintain the appropriate pH, P_{aCO_2} and P_{aO_2}.

Item CP9 $10 each

Nicotine Dependency Evaluation and Treatment

Helps you understand the physiologic effects of nicotine and the tests and questions used to evaluate dependency. Provides an understanding of nicotine, its effects on brain chemistry, its measurement in bodily fluids, and value of self-tests to determine addiction level. Also teaches about nicotine replacement and how to enhance it with behavioral counseling.

Item SC1 $10 each

Bedside Counseling of the Hospitalized Smoker

Prepares you for the role of a smoking cessation counselor to hospital inpatients by teaching assessment and bedside counseling. Help patients cope with nicotine withdrawal, increase motivation for permanent cessation, and understand the factors contributing to relapse.

Item SC2 $10 each

Authors in This Issue

Branson, Richard D 611, 671
Davis, Kenneth Jr 611
Douglas, Katherine A 630
Durbin, Charles G Jr 646
Fenwick, John 623
Hildebrandt, Jacob 669
Howard, William R 669
Jager, Kelly 623
Keenan, Jim 617
Layon, A Joseph 635
Lee, Tai-Shon 627
Madsen, Deborah 623
Mathewson, Hugh S 652, 667
McArdle, Philip 668
Monast, Ray 671
Nelson, Eva 635
Nelson, Vaughn 635
Piedalue, Fran 669
Pierson, David J 669
Polamreddy, Ramalinga 630
Porembka, David 611
Salyer, John W 617
Schiffman, Philip 667
Tweeddale, Martin 623
Vega, Henry 646
Wu, Yaw 627

Advertisers in This Issue

Allen & Hanburys 599, 600, 601
CNS Inc 601
DHD Diemolding Healthcare Div 594
Dräger Critical Care ..... Cover 3
HealthScan Products Inc 603, 605
HR Inc 607
Impact Medical Corp 610
Monaghan Medical Products Inc 608, 609
Respironics Inc 596
Sherwood Medical ..... Cover 4
Siemens Medical Systems ..... Cover 2

For faster service, FAX your reader service card to (609) 786-4415

81 AARC Membership Information

82 Respiratory Care Subscription Information

142 Allen & Hanburys Serevent

144 CNS Inc Breathe Right

94 DHD Diemolding Healthcare Div Incentive Spirometer

101 Dräger Critical Care Ventilator

119 HealthScan Products Peak Flow Meter

120 HealthScan Products Optihaler

106 HR Inc Sterilization Equipment

130 Impact Instrumentation Portable Ventilator

124 Monaghan Medical Peak Flow Meter

116 Respironics Inc BiPAP S/T-D Complete Hospital System

134 Sherwood Medical Pulmonary Function/Ventilation Monitor

103 Siemens Medical System Servo Ventilator 300

RESPIRATORY CARE

June Reader Service **Expires September 30, 1994**

Name _____ Ph# _____

Institution _____

Street _____

City/State/Zip _____

Please Circle No More Than 15 Items

80	81	82	83	84	85	86	87	88	89	90	91	92	93	94
95	96	97	98	99	100	101	102	103	104	105	106	107	108	109
110	111	112	113	114	115	116	117	118	119	120	121	122	123	124
125	126	127	128	129	130	131	132	133	134	135	136	137	138	139
140	141	142	143	144	145	146	147	148	149	150	151	152	153	154
155	156	157	158	159	160	161	162	163	164	165	166	167	168	169
170	171	172	173	174	175	176	177	178	179	180	181	182	183	184
185	186	187	188	189	190	191	192	193	194	195	196	197	198	199

I. Type of Instn/Practice
1 ❑ Hosp ≥ 500 or more beds
2 ❑ Hosp 300 to 499 beds
3 ❑ Hosp 200 to 299 beds
4 ❑ Hosp 100 to 199 beds
5 ❑ Hosp <100 or less bed
6 ❑ Skilled Nursing Facility
7 ❑ Home Care Practice
8 ❑ School

II. Department
A ❑ Respiratory Therapy
B ❑ Cardiopulmonary
C ❑ Anesthesia Service
D ❑ Emergency Dept

III. Specialty
1 ❑ Clinical Practice
2 ❑ Perinatal Pediatrics
3 ❑ Critical Care
4 ❑ Clinical Research
5 ❑ Pulmonary Function Lab
6 ❑ Home Care/Rehab
7 ❑ Education
8 ❑ Management

IV. Position
A ❑ Dept Head
B ❑ Chief Therapist
C ❑ Supervisor
D ❑ Staff Technician
E ❑ Staff Therapist
F ❑ Educator
G ❑ Medical Director
H ❑ Anesthesiologist
I ❑ Pulmonologist
J ❑ Other MD
K ❑ Nurse

V. Are you a member of the AARC?
1 ❑ Yes 2 ❑ No

RESPIRATORY CARE

June Reader Service **Expires September 30, 1994**

Name _____ Ph# _____

Institution _____

Street _____

City/State/Zip _____

Please Circle No More Than 15 Items

80	81	82	83	84	85	86	87	88	89	90	91	92	93	94
95	96	97	98	99	100	101	102	103	104	105	106	107	108	109
110	111	112	113	114	115	116	117	118	119	120	121	122	123	124
125	126	127	128	129	130	131	132	133	134	135	136	137	138	139
140	141	142	143	144	145	146	147	148	149	150	151	152	153	154
155	156	157	158	159	160	161	162	163	164	165	166	167	168	169
170	171	172	173	174	175	176	177	178	179	180	181	182	183	184
185	186	187	188	189	190	191	192	193	194	195	196	197	198	199

I. Type of Instn/Practice
1 ❑ Hosp ≥ 500 or more beds
2 ❑ Hosp 300 to 499 beds
3 ❑ Hosp 200 to 299 beds
4 ❑ Hosp 100 to 199 beds
5 ❑ Hosp <100 or less beds
6 ❑ Skilled Nursing Facility
7 ❑ Home Care Practice
8 ❑ School

II. Department
A ❑ Respiratory Therapy
B ❑ Cardiopulmonary
C ❑ Anesthesia Service
D ❑ Emergency Dept

III. Specialty
1 ❑ Clinical Practice
2 ❑ Perinatal Pediatrics
3 ❑ Critical Care
4 ❑ Clinical Research
5 ❑ Pulmonary Function Lab
6 ❑ Home Care/Rehab
7 ❑ Education
8 ❑ Management

IV. Position
A ❑ Dept Head
B ❑ Chief Therapist
C ❑ Supervisor
D ❑ Staff Technician
E ❑ Staff Therapist
F ❑ Educator
G ❑ Medical Director
H ❑ Anesthesiologist
I ❑ Pulmonologist
J ❑ Other MD
K ❑ Nurse

V. Are you a member of the AARC?
1 ❑ Yes 2 ❑ No

Information Requests or Change of Address

Please complete the card below

AARC Membership No. _____

Old Address

Name _____

Street _____

City/State/Zip _____

New Address

Street _____

City/State/Zip _____

Check the boxes below for information from the AARC

- ❑ Change of address
- ❑ AARC Membership Info
- ❑ AARC Catalog
- ❑ AARC Position Statement

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 604 RIVERTON, NJ

POSTAGE WILL BE PAID BY ADDRESSEE

AARC PUBLICATIONS
PO BOX 1856
RIVERTON NJ 08077-9456

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 604 RIVERTON, NJ

POSTAGE WILL BE PAID BY ADDRESSEE

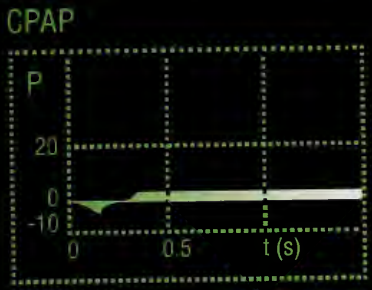
AARC PUBLICATIONS
PO BOX 1856
RIVERTON NJ 08077-9456

Return Address

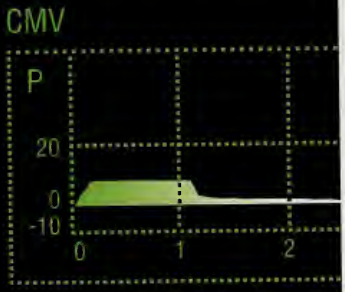
Place
Stamp
Here

AMERICAN ASSOCIATION FOR
RESPIRATORY CARE
11030 ABLES LN
DALLAS TX 75229-4593

Use these cards to request information from the AARC or advertisers in this issue.



Occlusion-pressure



Intrinsic PEEP

Always A Step Ahead!

Evita makes work of breathing even easier!

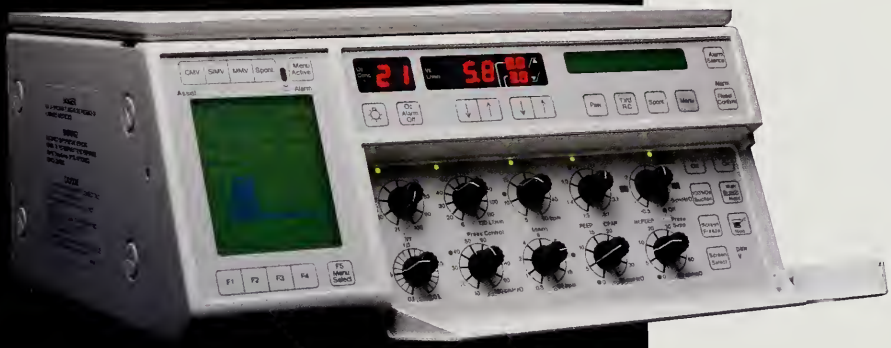
Now **Dräger** provides you with two more powerful tools to optimize weaning of your patients.

Introducing **Flowtrigger** without increase of expiratory resistance, combined with **P01 measurement** to determine the patients ventilatory drive.

To extend monitoring capabilities Evita now includes the ability to measure **Intrinsic Peep** with the display of **Trapped Volume.**

With **Dräger** you can stay one step ahead in providing safe, patient friendly ventilation. For the difference your patients can feel, choose...

Dräger: Technology for Life



Flowtrigger

Dräger

Technology for life

4101 Pleasant Valley Road Suite 100 Chantilly, VA 22021
Tel (703) 817-0100 Fax (703) 817-0101

Circle 101 on reader service card

RESPIRADYNE® II PLUS

PULMONARY FUNCTION/VENTILATION MONITOR

Graphic Printouts...Multi-Patient Memory...and Easy to Use

Results-Oriented Features At Cost Effective Prices

■ New Graphic Forced Vital Capacity (FVC) document printout of Flow vs Volume and Volume vs Time ■ New 10 patient memory with 8 pre-bronchodilator and 8 post-bronchodilator tests per patient and automatic calculation of % change ■ New customizing software package ■ New Slow Vital Capacity (SVC) monitoring ■ Automatic determination of "best test" ■ Knudson, ITS and ECCS reference nomograms ■ Easy to operate

Performs A Complete Range Of Test Measurements

Forced Exhalation Parameters

■ Forced Vital Capacity (FVC) ■ Forced Expiratory Volume in One Second (FEV_1) ■ FEV_1/FVC Ratio ■ FVC Time ■ Peak Flow ■ Forced Expiratory Flow Between 25% and 75% of Vital Capacity ($FEF_{25-75\%}$) ■ Percent Extrapolated Volume ($Vol._{EXTRA\%}$)

Weaning/Extubation Parameters

■ Respiratory Rate (RR) ■ Tidal Volume (TV) ■ Minute Volume (MV) ■ Slow Vital Capacity (SVC) ■ Maximum Voluntary Ventilation (MVV) ■ Negative Inspiratory Force (NIF)

For further information, call: 1-800-325-7472 (outside Missouri) 1-800-392-7318 (in Missouri)

Sherwood MEDICAL
ST. LOUIS, MO. 63103 U.S.A.

Circle 134 on reader service card